The Brain in Dissociative Identity Disorder: Reactions to Subliminal Facial Stimuli and a Task-Free Condition

Thesis
presented to the Faculty
of
Arts at the University of Zurich

for the degree of Doctor of Philosophy

by

Yolanda Schlumpf
of Mönchaltorf ZH, Switzerland

Accepted in the fall semester 2012
on the recommendation of

Prof. Dr. Lutz Jäncke
Prof. Dr. Björn Rasch

Zurich, 2013

Contents

Acknowledgments

I wish to express my thanks to all of those who helped me in accomplishing this work.

First of all I would like to thank my doctoral advisor Prof. Lutz Jäncke. He firstly attracted my attention for neuroscience and gave me the opportunity to combine my interest in clinical psychology with brain research methods. I am very grateful for his scientific guidance and mentoring, and particularly for giving me the opportunity to carry out this dissertation on a topic of my choice.

I would like to convey my gratitude to Dr. Ellert Nijehuis for his inspiration and the enriching discussions of the clinical findings. I like to express further greatest thanks to Dr. Simone Reinder who introduced me in a new field of research. Thank you both for your effort and support.

This work would not have been possible without the professional clinical support of Katharina Weder and Eva Zimmermann. I very appreciate the excellent cooperation we had and the possibility to gain insights into the therapeutic work with dissociative identity disorder patients.

I like to express great thanks to all coworkers and colleagues of the division of Neuropsychology at the University of Zurich. I have truly enjoyed the friendly working environment. I am very thankful for all fruitful discussions and instrumental supports. I am especially grateful to my office colleague, Dr. Franciscus Liem, for the warm and stimulating working atmosphere during my entire PhD period.

At this point, I would like to thank Prof. Dr. Björn Rasch for his unconditioned acceptance to co-examine this dissertation.

I am indebted to Dr. Roger Lüchinger and Dr. Matthias Van Osch for their willingness to support me and their patience in coaching me MR physics.

Special thanks go to the patients and their therapists. I am deeply impressed by their motivation and effort to participate in the study. I appreciate very much their confidence and the experiences I made during the measurements.

I express my gratitude to the financial support of the University of Zurich (Forschungskredit), which made possible the study presented in this work.

Finally, I would like to express a very special thank to all my friends for keeping faith in me and to my neighbours for the relaxing dinners. My deepest thanks go to my family for their love and support.

Summary

Dissociative identity disorder (DID) is the most complex dissociative disorder. The prevalence of DID in community samples is estimated to be between 0.4% (Akyuz, Dogan, Sar, Yargic, & Tutkun, 1999) and 1.5% (Johnson, Cohen, Kasen, & Brook, 2006). The prevalence in samples of psychiatric patients ranges from approximately 1% (Gast, Rodewald, Nickel, & Emrich, 2001; Rifkin, Ghisalbert, Dimatou, Jin, & Sethi, 1998) and 2% (Friedl & Draijer, 2000), to 5.4% (Tutkun, et al., 1998) and 6% (Foote, Smolin, Kaplan, Legatt, & Lipschitz, 2006).

Proponents of the traumagenic view state that DID develops in the context of severe and chronic trauma, often beginning in the early childhood (Dalenberg, et al., 2012; Dell, 2006; Gleaves, 1996; Lyons-Ruth, Dutra, Schuder, & Bianchi, 2006; Nijenhuis, Van der Hart, & Steele, 2002, 2004; Ogawa, Sroufe, Weinfield, Carlson, & Egeland, 1997; Trickett, Noll, & Putnam, 2011; Van der Hart, Nijenhuis, & Steele, 2006). According to this view, the Theory of Structural Dissociation of the Personality (TSDP) (Nijenhuis & Den Boer, 2009; Nijenhuis, et al., 2002; Van der Hart, et al., 2006) proposes that DID is a severe form of posttraumatic stress disorder (PTSD) and encompasses different types of dissociative parts of the personality. A primary classification is “Emotional Part” (EP) and “Apparently Normal Part” (ANP). Switching between these dissociative parts is a major characteristic of DID. Clinical observations suggest that as EP, DID patients recall traumatic experiences and are fixated on these memories. As ANP, DID patients claim a degree of amnesia for trauma memories and are detached from the trauma.

A previous symptom-provocation study demonstrated that ANP and EP in DID have different psychophysiological and neural reaction patterns to personalized trauma scripts (Reinders, et al., 2003; Reinders, Nijenhuis, et al., 2006). In this study, as EP compared to ANP, DID patients were psychophysiologically aroused and showed significant activation in many brain areas also observed in PTSD patients while they were confronted with a personalized trauma script. In contrast, as ANP, DID patients yielded a brain activation pattern similar to patients with depersonalization disorder and PTSD patients with negative dissociative symptoms to trauma-related stimuli. Thus, in line with the hypotheses derived from the TSDP,

as EP, patients were emotionally engaged in the trauma script, and as ANP, these patients were detached from the trauma-related stimulus.

Whereas most theories of DID include traumatization as one of the causal factors of the disorder, the sociocognitive model of DID entails the idea that the disorder is caused by suggestion, fantasy proneness, and role-playing (Giesbrecht, Lynn, Lilienfeld, & Merckelbach, 2008; Lilienfeld, et al., 1999; Lynn, Lilienfeld, Merckelbach, Giesbrecht, & Van der Kloet, 2012; Merckelbach, Horselenberg, & Schmidt, 2002; Merckelbach & Muris, 2001; Merskey, 1992; Piper & Merskey, 2004; Spanos, 1994). Inconsistent with this view, DID patients were not particularly fantasy prone, and low and high fantasy prone healthy participants did not generate the patterns of psychophysiological and neural activation that marked these parts in DID (Reinders, Willemsen, Vos, Den Boer, & Nijenhuis, 2012).

Two experiments were conducted as a part of the present work. Both focused on the investigation of ANP and EP in DID patients as two prototypical dissociative parts of the personality. The current thesis addressed the questions of whether ANP and EP process threatening stimuli differently already at a preconscious level and, furthermore, whether perfusion differences between ANP and EP exist in a task-free condition (i.e., resting-state).

In Experiment 1, 15 female DID patients and 15 matched, mentally healthy, female actors (controls) were confronted with masked (i.e., subliminally presented) neutral and angry faces while their brain function was monitored using functional magnetic resonance imaging (fMRI). Both, DID patients and actors, underwent consecutively subliminal face presentation once as ANP and once as EP. Actors were instructed and motivated to mimic these dissociative parts of the personality in order to involve a psychobiological comparison between genuine and simulated DID patients. The faces were presented for 16.7 msec, and a mask proceeded and followed face presentation and ensured that the faces could not be seen consciously. Each mask contained a colored dot (yellow or turquoise). The color of the dot on the masks that preceded the faces was different from the color of the dot on the masks that followed these pictures. The participants were instructed to immediately press a button when they noticed that the color of the dot had changed, and their reaction times (RTs) were measured. The longer RTs for the patients' EP compared to the patients' ANP indicate that as EP, DID patients were fixated on the subliminally

presented faces. The longest RTs could be observed in EP following neutral faces and are in line with the neural data showing the most prominent finding in the neutral face condition aswell. EP in DID compared to EP in actors showed increased activity as reaction to neutral faces in face-sensitive areas (i.e., occipito-temporal junction) and in the dorsal brainstem. These findings indicate that as EP, DID patients deeply engaged in subliminally presented faces, particularly in neutral faces, and were psychophysiologically aroused by these faces. EP's activity in motor-related areas (i.e., pre-supplementary motor area, precentral gyrus) furthermore suggests defensive reactions to perceived threat. As ANP, DID patients were associated with less brain activity all over the brain in both face conditions, which suggests less involvement in the subliminally presented faces. As predicted by the TSDP, actors were not able to mimic DID patients neither as ANP nor as EP in a behavioral and neural sense.

Based on these findings, a major clinical implication is that therapists of DID patients must be emotionally and behaviorally engaged, as therapeutic neutrality might scare the patient, particularly as EP, and might trigger defensive and emotional reactions.

Experiment 2 consisted of the same sample as Experiment 1. In Experiment 2, the subjects' resting-state function as ANP and EP was recorded using an arterial spin labeling (ASL) MR sequence. In this task-free condition, brain activation patterns in DID were dependent on the type of dissociative part that was dominant during the measurement. Compared to ANP, EP showed increased perfusion in the postcentral gyrus (i.e., somatosensory cortex), dorsomedial prefrontal cortex, and motor-related areas (i.e., pre-supplementary motor area, precentral gyrus, posterior midcingulate cortex). This perfusion pattern suggests that as EP compared to ANP, DID patients were attending more to their self-state and somatosensory sensations, which might have triggered defense motor reactions. As ANP compared to EP, patients yielded elevated bilateral thalamus activity, which is in line with previous studies showing that negative dissociative symptoms are related to increased thalamic functioning. Fitting their reported role-playing strategies, actors activated brain structures involved in visual mental imagery and empathizing feelings.

In conclusion, the findings of Experiment 1 and Experiment 2 are consistent with the TSDP and inconsistent with the idea that DID is caused by suggestion,

fantasy proneness, and role-playing, as actors were not able to mimic the patterns of brain function typically exhibited by DID patients.

Zusammenfassung

Die dissoziative Identitätsstörung (DIS) ist die schwerste dissoziative Störung. Die Prävalenz der DIS in der Normalbevölkerung liegt zwischen 0.4% (Akyuz, et al., 1999) und 1.5 % (Johnson, et al., 2006). Die Prävalenz in klinischen Stichproben reicht von ca. 1% (Gast, et al., 2001; Rifkin, et al., 1998) und 2% (Friedl & Draijer, 2000) bis 5.4% (Tutkun, et al., 1998) und 6% (Foote, et al., 2006).

Anhänger der traumabedingten Sichtweise behaupten, dass die Entstehung einer DIS auf schwere und chronische Traumatisierungen, meistens beginnend in der frühen Kindheit, zurückzuführen ist (Dalenberg, et al., 2012; Dell, 2006; Gleaves, 1996; Lyons-Ruth, et al., 2006; Nijenhuis, et al., 2002, 2004; Ogawa, et al., 1997; Trickett, et al., 2011; Van der Hart, et al., 2006). In Übereinstimmung mit dieser Sichtweise geht die Theorie der Strukturellen Dissoziation der Persönlichkeit (TSDP) (Nijenhuis & Den Boer, 2009; Nijenhuis, et al., 2002; Van der Hart, et al., 2006) davon aus, dass die DIS eine schwere Form einer posttraumatischen Belastungsstörung (PTBS) ist und mit unterschiedlichen Arten von dissoziativen Persönlichkeitsanteilen einhergeht. Eine grundlegende Unterscheidung besteht zwischen dem “Emotionalen Persönlichkeitsanteil” (EP) und dem “Anscheinend Normalen Persönlichkeitsanteil” (ANP). Der Wechsel zwischen diesen dissoziativen Persönlichkeitsanteilen stellt ein Hauptmerkmal der DIS dar. Klinische Beobachtungen legen nahe, dass DIS-Patienten als EP über ein Traumagedächtnis verfügen und auf diese traumatischen Erinnerungen fixiert sind. Als ANP hingegen weisen DIS-Patienten eine vollständige oder partielle Amnesie bezüglich traumatischer Erfahrungen auf oder erleben diese als nicht zu ihnen gehörig.

In einer Symptomprovokationsstudie konnte gezeigt werden, dass DIS-Patientinnen als ANP und EP unterschiedliche psychophysiologische und neuronale Muster als Reaktion auf invidualisierte Trauma-Skripts aufweisen (Reinders, et al., 2003; Reinders, Nijenhuis, et al., 2006). In dieser Studie waren DIS-Patientinnen als EP im Vergleich zum ANP psychophysiologisch erregt und zeigten eine erhöhte Aktivierung in Gehirnarealen, die auch bei PTBS-Patienten bei der Konfrontation mit individualisierten Traumaskripts beobachtet werden konnte. Im Gegensatz dazu zeigten DIS-Patientinnen als ANP ein Gehirnaktivierungsmuster, welches demjenigen von Patienten mit einer Depersonalisationsstörung und PTBS-Patienten mit

negativen dissoziativen Symptomen als Reaktion auf Traumastimuli glich. Somit ist festzuhalten, dass in Übereinstimmung mit den Hypothesen, die basierend auf der TSDP formuliert wurden, Patientinnen als EP emotional in die Traumaskripts involviert waren, währenddessen diesselben Patientinnen als ANP die Traumastimuli als nicht zu sich gehörig verarbeiteten.

Während die meisten Theorien zur DIS davon ausgehen, dass Traumatisierungen dieses Störungsbild verursachen, basiert das soziokognitive Modell auf der Behauptung, dass die DIS durch Suggestion, Fähigkeit zum Fantasieren und Rollenspiel erklärt werden kann (Giesbrecht, et al., 2008; Lilienfeld, et al., 1999; Lynn, et al., 2012; Merckelbach, Horselenberg, et al., 2002; Merckelbach & Muris, 2001; Merskey, 1992; Piper & Merskey, 2004; Spanos, 1994). Im Widerspruch zu dieser Sichtweise konnte beobachted werden, dass DIS-Patientinnen keine erhöhte Neigung zum Fantasieren aufweisen, und dass weder gesunde Probandinnen mit einer tiefen noch mit einer hohen Neigung zum Fantasieren die psychophysiologischen und neuronalen Reaktionsmuster von echten DIS-Patientinnen hervorrufen konnten (Reinders, et al., 2012).

Im Rahmen dieser Arbeit wurden zwei Experimente durchgeführt. Beide verfolgten das Ziel, ANP und EP als zwei prototypische dissoziative Anteile der Persönlichkeit von DIS-Patientinnen zu erforschen. So ging die vorliegende Doktorarbeit den Fragen nach, ob ANP und EP bedrohliche Stimuli bereits auf einer vorbewussten Ebene unterschiedlich verarbeiten und ob Unterschiede in der Gehirndurchblutung zwischen ANP und EP in einem Setting ohne externe Aufgabenstellung (Ruhezustand) beobachted werden können.

In Experiment 1 wurden 15 DIS-Patientinnen und 15 parallelisierte, psychisch gesunde Schauspielerinnen mit maskierten (d.h. subliminal präsentierten) neutralen und wütenden Gesichtern konfrontiert. Während der subliminalen Gesichterpräsentation wurde die Gehirnaktivierung mittels funktioneller Magnetresonanztomographie (fMRT) aufgezeichnet. Sowohl die DIS-Patientinnen als auch die Schauspielerinnen durchliefen das Experiment einmal als ANP und einmal als EP. Die Schauspielerinnen wurden instruiert und motiviert, diese dissoziativen Persönlichkeitsanteile zu imitieren, um echte und simulierte DIS-Patientinnen auf psychobiologischer Ebene miteinander vergleichen zu können. Die Präsentationszeit der Gesichter betrug 16.7 Millisekunden. Eine Maske wurde sowohl unmittelbar vor,

als auch unmittelbar nach den subliminalen Gesichtern eingeblendet und bewerkstelligte, dass die Gesichter nicht bewusst wahrgenommen werden konnten. Auf jeder Maske war ein farbiger Punkt (gelb oder türkis) zu sehen. Die Farbe des Punktes auf den Masken, die vor den Gesichtern gezeigt wurden, war jeweils eine andere als die Farbe des Punktes auf den Masken, die auf diese Bilder folgten. Die Teilnehmerinnen wurden dahingehend instruiert, so schnell wie möglich eine Taste zu drücken, sobald sie einen Farbwechsel bemerkten. Dabei wurden ihre Reaktionszeiten gemessen. Die Patientinnen zeigten als EP im Vergleich zum ANP längere Reaktionszeiten, was darauf hinweist, dass die DIS-Patientinnen als EP auf die subliminal präsentierten Gesichter fixiert waren. Die längsten Reaktionszeiten konnten beim EP in der neutralen Gesichtsbedingung beobachtet werden. Dieser Befund steht in Übereinstimmung mit den neuronalen Daten, da auf neuronaler Ebene der bedeutendste Befund ebenfalls in der neutralen Gesichtsbedingung beobachtet werden konnte. DIS-Patientinnen wiesen als EP im Vergleich zu simulierten EPs in Reaktion auf neutrale Gesichter eine erhöhte Aktivierung in Arealen auf, die an der Gesichtswahrnehmung beteiligt sind (occipito-temporaler Übergangsbereich). Ebenso konnte eine erhöhte Aktivierung im dorsalen Hirnstamm beobachtet werden. Diese Befunde weisen darauf hin, dass DIS-Patientinnen als EP intensiv in die subliminal präsentierten Gesichter, insbesondere in neutrale Gesichter, involviert waren und durch diese Gesichter psychophysiologisch erregt wurden. Des Weiteren kann die Aktivierung der EPs in motorischen Arealen (prä-supplementär motorisches Areal, präzentraler Gyrus) als Verteidigungsreaktion auf wahrgenommene Bedrohung interpretiert werden. Als ANP zeigten DIS-Patientinnen in beiden Gesichtsbedingungen eine generell niedrigere Aktivierung im ganzen Gehirn. Dies lässt vermuten, dass Patientinnen als ANP weniger in die subliminal präsentierten Gesichter involviert waren. Wie auf der TSDP basierend vorhergesagt gelang es den Schauspielerinnen weder als ANP noch als EP nicht, die DIS-Patientinnen auf behavioraler und neuronaler Ebene zu imitieren.

Eine wichtige therapeutische Implikation dieser Befunde ist, dass Therapeuten von DIS-Patienten eine emotionale und verhaltensmässige Beteiligung ausdrücken sollten, da therapeutische Neutralität die Patienten, und hierbei insbesondere als EPs, verängstigen könnte. Und dies könnte wiederum Verteidigungs- und emotionale Reaktionen auslösen.

Experiment 2 wurde mit der gleichen Stichprobe wie in Experiment 1 durchgeführt. In Experiment 2 wurden die Teilnehmerinnen als ANP und EP im Ruhezustand mit einer Arterial Spin Labeling (ASL) MR-Sequenz gemessen. Die Ergebnisse dieses Experimentes weisen darauf hin, dass in einem Setting, in der keine externe Aufgabenstellung vorhanden ist, das Gehirnaktivierungsmuster von DIS-Patientinnen von der Art des dissoziativen Persönlichkeitsanteils abhängt, der während der Messung anwesend ist. Im Vergleich zum ANP zeigte der EP erhöhte Durchblutung im postzentralen Gyrus (somatosensorischer Kortex), dosomedialen präfrontalen Kortex und in Motorarealen (prä-supplementär motorisches Areal, präzentraler Gyrus, posteriorer midzingulärer Kortex). Dieses Durchblutungsmuster lässt vermuten, dass DIS-Patientinnen als EP im Vergleich zum ANP stärker mit der Beobachtung ihres eigenen Zustandes und den somatosensorischen Empfindungen beschäftigt waren, was möglicherweise zur Auslösung von motorischen Verteidigungsreaktionen führte. Als ANP im Vergleich zum EP zeigten die Patientinnen eine erhöhte bilaterale Thalamusaktivität. Dieser Befund deckt sich mit früheren Studien, in denen ebenfalls negative dissoziative Symptome mit einer erhöhten Thalamusfunktion einhergingen. Schauspielerinnen aktivierten Gehirnstrukturen, die mit visueller Vorstellung und empathischem Einfühlen assoziiert werden können. Dieses Aktivierungsmuster steht in Übereinstimmung mit den von den Schauspielerinnen zur Ausübung des Rollenspiels berichteten Strategien.

Zusammenfassend kann festgehalten werden, dass es Schauspielerinnen nicht gelungen ist, die Funktionsweise des Gehirns von DIS-Patientinnen zu imitieren. Die Ergebnisse von Experiment 1 und Experiment 2 stehen mit der TSDP in Übereinstimmung, widersprechen jedoch der Idee, dass die DIS durch Suggestion, Fähigkeit zum Fantasieren oder Rollenspiel erklärt werden kann.

Abbreviations

A	Angry faces
AB	Attentional bias
aMCC	Anterior midcingulate cortex
ANP	Apparently Normal Part of the personality
ASL	Arterial spin labeling
BOLD	Blood-oxygenated-level dependent
CON	Control group
CONanp	Simulated ANP
CONep	Simulated EP
DID	Dissociative identity disorder/Patient group
DIDanp	Genuine ANP
DIDep	Genuine EP
DMN	Default mode network
DMPFC	Dorsomedial prefrontal cortex
dPCC	Dorsal posterior cingulate cortex
EP	Emotional Part of the personality
fMRI	Functional magnetic resonance imaging
GM	Gray matter
kE	Cluster size
MNI	Montreal Neurological Institute
MNS	Mirror neuron system
N	Neutral faces
OFC	Orbitofrontal cortex
PET	Positron Emission Computed Tomography
PCC	Posterior cingulate cortex
pMCC	Posterior midcingulate cortex
PTSD	Posttraumatic stress disorder
Pre-SMA	Pre-supplementary motor area
rCBF	Regional cerebral blood flow
RT	Reaction time

S	Scramble stimuli
SPECT	Single Photon Emission Computed Tomography
STS	Sulcus temporalis superior
TSDP	Theory of Structural Dissociation of the Personality
Type	Type of dissociative part of the personality

1. Introduction

Dissociative identity disorder (DID) is the most complex and severe dissociative disorder and is characterized by the appearance of severe dissociative symptoms, such as amnesia, derealisation, depersonalisation, identity confusion, and identity alteration (ISSD, 1997). The prevalence of DID in community samples is estimated to be between 0.4% (Akyuz, et al., 1999), 1.1% (Sar, Akyuz, & Dogan, 2007), and 1.5% (Johnson, et al., 2006). The prevalence rates for DID found in samples of psychiatric patients ranged from approximately 1% (Gast, et al., 2001; Rifkin, et al., 1998) and 2% (Friedl & Draijer, 2000), to 5.4% (Tutkun, et al., 1998) and 6% (Foote, et al., 2006). DID has gained a lot of attention for over more than a century, and is increasingly acknowledged as a diagnostic entity. Although there is a growing research literature, neuroimaging studies in DID are sparse, and there is still much unknown about the neural mechanisms involved in DID.

This thesis focuses on several aspects of functional magnetic resonance imaging to investigate neurophysiological characteristics of single dissociative parts of the personality in DID. After a short introduction in chapter 1, chapter 2 addresses the question what dissociation is and outlines two opposing theories of the aetiology of DID. This chapter also summarizes previous research, which was derived from the two models. Based on these theoretical and empirical grounds, the investigation of the sense of self in DID is discussed. Chapter 3 describes the study sample and gives a short introduction into the methods used in the experiments conducted as a part of the present doctoral thesis. Chapter 4 outlines the aims of Experiment 1 and Experiment 2 and emphasizes the relevance of this thesis. The two experiments including the results are described in chapter 5, and chapter 6 concludes the thesis with a summary of the results and a general discussion.

2. Theoretical background

2.1. Dissociation and traumatizing events

Several theories have proposed that complex dissociative disorders, such as DID, tend to develop in the context of severe and chronic childhood traumatization, which includes chronic neglect and abuse by significant others. Numerous independent studies support this view. For example, relations between attachment disruption and dissociation two decades later have been documented (Dutra, Bureau, Holmes, Lyubchik, & Lyons-Ruth, 2009; Lyons-Ruth, et al., 2006; Ogawa, et al., 1997), and in many retrospective studies (Dell & O'Neil, 2009; Gleaves, 1996; Nijenhuis, 2004; Van der Hart, et al., 2006), relations between chronic traumatization in childhood and DID have been found. Reported traumatization in DID has been verified in a substantial number of cases (Lewis, Yeager, Swica, Pincus, & Lewis, 1997). Many definitions of dissociation have been proposed, and it was commonly defined as an important survival mechanism, which provides a strategy of storing trauma-related knowledge in a state-dependent manner. But no consensus on the phenomena has been reached so far. To resolve the current conceptual confusion regarding dissociation arising out of trauma, a new definition has been proposed (Nijenhuis & Van der Hart, 2011):

> Dissociation in trauma entails a division of an individuals's personality, that is, of the dynamic, biopsychosocial system as a whole that determines his or her characteristic mental and behavioural actions. This division of personality constitutes a core feature of trauma. It evolves when the individual lacks the capacity to integrate adverse experiences in part or in full, can support adaptation in this context, but commonly also implies adaptive limitations. The division involves two or more insufficiently integrated dynamic but excessively stable subsystems. These subsystems exert functions, and can encompass any number of different mental and behavioural actions and implied states. These subsystems and states can be latent, or activated in a sequence or in parallel. Each dissociative subsystem, that is, dissociative part of the personality minimally includes its own, at least rudimentary first-person perspective. As each dissociative part, the individual can interact with other

> dissociative parts and other individuals, at least in principle. Dissociative parts maintain particular psychobiological boundaries that keep them divided, but that they can in principle dissolve. Phenomenologically, this division of the personality manifests in dissociative symptoms that can be categorized as negative (functional losses such as amnesia and paralysis) or positive (intrusions such as flashbacks or voices), and psychoform (symptoms such as amnesia, hearing voices) or somatoform (symptoms such as anesthesia or tics). (p. 418)

This definition stresses the lack of integration within the personality due to potentially traumatizing events, which overwhelm or lower the exposed individuals' integrative capacity. The definition goes beyond the idea that dissociation is a simple protective mechanism. In contrast to the dissociative parts of the personality who can be characterized by negative dissociative symptoms, those who manifest positive dissociative symptoms are completely exposed to re-experiencing the traumatic past.

2.2. The Theory of Structural Dissociation of the Personality

The hypotheses of the present study are derived from the Theory of Structural Dissociation of the Personality (TSDP) (Nijenhuis & Den Boer, 2009; Nijenhuis, et al., 2002; Van der Hart, et al., 2006). According to this theory, DID involves different types of dissociative, that is, insufficiently integrated subsystems or parts of the personality as a whole biopsychosocial system. The basic structural trauma-related dissociation is between the "Emotional Part" (EP) and "Apparently Normal Part" (ANP). ANP is largely mediated by evolutionary prepared action systems for functioning in daily life. As ANP, DID patients may claim a degree of amnesia for traumatic memories, do not or not sufficiently personify traumatic experiences and memories, and attempt to mentally and behaviorally avoid trauma-related stimuli. They are to some degree depersonalized and bodily numbed, thus, ANP can be associated with negative dissociative symptoms. In contrast, EP is primarily mediated by action systems for bodily defense to potential threat and can be distinguished in subtypes (Nijenhuis & Den Boer, 2009). One subtype is fixed in traumatic memories and engages in active mammalian defenses to a major threat (e.g., freeze, flight,

attachment cry). In response to perceived or real threat, they manifest strong emotional and sensorimotor reactions (i.e., hyperarousal), which can be described as positive dissociative symptoms. The other subtype engages in passive mammalian defense (playing dead), which implies emotional and bodily anesthesia. In the two experiments included in this present dissertation, we only investigated the former subtype, which will be referred to as EP in the rest of the text.

According to the TSDP (Van der Hart, et al., 2006), dissociative disorders can be described on a continuum from simple forms to complex forms of dissociative disorders. In primary structural dissociation, which is characteristic of posttraumatic stress disorder (PTSD) and simple forms of somatoform dissociative disorders (i.e., dissociative disorders of sensation and movement), there is one ANP and one EP. Secondary structural dissociation, which marks complex PTSD and many cases of dissociative disorder not otherwise specified (DDNOS), involves one ANP and multiple EPs. Tertiary structural dissociation is the organization characterizing DID and encompasses multiple ANPs and multiple EPs.

2.2.1. Supportive research findings: Reactions to supra- and subliminal threatening cues

A previous Positron Emission Computed Tompgraphy (PET) study shows strong evidence that ANP and EP can be associated with different physiological and neural patterns as reaction to trauma-related cues (Reinders, et al., 2003; Reinders, Nijenhuis, et al., 2006). In this study, DID patients listened as ANP and EP to audiotaped descriptions of a traumatic memory that was only autobiographical for EP. The findings support the hypotheses derived from the TSDP that as EP, DID patients are fixed in traumatic memories and have hyperaroused psychobiological reactions to reminders of traumatic experiences, and that as ANP, they react to trauma-related cues in a depersonalized and detached manner (i.e., hypoarousal). The study of Reinders et al. (2003) and Reinders, Nijenhuis et al. (2006) will be described in more details in the empirical part (chapter 5).

A second study used backward masking (i.e., masked/subliminal presentation of emotional facial stimuli) to address the question of whether these differences between ANP and EP already exist at a preconscious level (Hermans, Nijenhuis, Van Honk, Huntjens, & Van der Hart, 2006). ANP and EP were for 25 msec exposed to

neutral faces and angry faces (i.e., potent conditioned threat stimuli after sexual and physical abuse). They were instructed to mention the color of the masks following the faces. ANP but not EP showed a significantly shorter reaction time (RT) in color naming the masks that followed the angry faces compared to masks that followed the neutral faces. This RT pattern indicates that ANP but not EP engages in preconscious mental avoidance of perceived threat.

The automaticity of phobic responses in PTSD patients has been documented in imaging studies using backward masking of trauma-related stimuli (Armony, Corbo, Clement, & Brunet, 2005; Bryant, et al., 2008; Hendler, et al., 2003; Rauch, et al., 2000). Experiment 1, conducted as a part of the present dissertation (see chapter 5), is the first research project that used this paradigm to examine neural activity in DID patients in response to fear-related stimuli presented below the threshold of conscious awareness. The backward masking technique will be described in more detail in the method section (chapter 3).

2.3. The sociocognitive model of dissociative identity disorder

A rival theory to the TSDP is the sociocognitive theory of DID, which holds that DID involves fantasy proneness, suggestibility, and role-enactment rather than a history of childhood trauma (Giesbrecht, et al., 2008; Lilienfeld, et al., 1999; Lynn, et al., 2012; Merckelbach, Horselenberg, et al., 2002; Merckelbach & Muris, 2001; Merskey, 1992; Piper & Merskey, 2004; Spanos, 1994). This assumption is related to the iatrogenic position. Iatrogenic proponents assert that DID is a creation of (possibly suggestive) psychotherapeutic treatment inducing false memories (Piper & Merskey, 2004). In this view, the psychotherapist plays a critical role, and DID is not regarded as a valid psychiatric disorder.

2.3.1. Contradicting research findings: Suggestion, fantasy proneness, and role-playing

Nijenhuis and Reinders found that women with DID are less fantasy prone than patients with borderline personality disorder and not more fantasy prone than female high school students, university teachers, and university personnel (Reinders, et al., 2012). Reinders et al. (2012) also observed that neither high nor low fantasy prone

mentally healthy women who were instructed and motivated to simulate ANP and EP convincingly mimicked the reaction patterns of ANP and EP in women with DID in a psychophysiological and neural sense. In the Hermans et al. (2006) study, described above, healthy controls instructed to role-play ANP and EP showed the reverse RT patterns compared to ANP and EP of genuine DID patients. That is, as ANP, the actors tended to react like EP in DID patients, and as EP like ANP in these patients. In line with the TSDP, these findings show strong evidence that DID cannot be explained by suggestion, fantasy proneness, or role-playing. Nevertheless, fantasy proneness and applied fantasy can play a role in the development of phenomenal self-models of dissociative parts (e.g., the idea of a dissociative part of a female patient that he is male) (Nijenhuis and Reinders, see Supporting Information S1 to Reinders, et al., 2012).

To date, no study could prove that traumatic memories can be experimentally induced. Research and clinical observations support the hypothesis that traumatic memories have a poor narrative quality, are nonverbal and fragmentary in nature, and strongly involve sensorimotor features (Brewin, 2001; Van der Kolk, 1997). Findings of false memory studies conducted so far (Loftus, Coan, & Pickrell, 1996; Loftus & Ketcham, 1994; Loftus & Pickrell, 1995) are restricted to manipulations of narrative memories (i.e., explicit verbal memories) and, thus, cannot be generalized to the sensorimotor and highly emotional trauma memories of DID patients. Furthermore, authors theoretically strongly biased against the existence of DID have not done a single study with DID patients. Their findings rely on self-reports of students (Merckelbach, Muris, Rassin, & Horselenberg, 2000; Merckelbach, Rassin, & Muris, 2000) and psychiatric patients suffering from other mental disorders (Merckelbach, à Campo, Hardy, & Giesbrecht, 2005).

2.4. Resting-state functional magnetic resonance imaging in dissociative identity disorder patients

According to the TSDP (Van der Hart, et al., 2006), dissociative parts of the personality include at least a rudimentary form of first-person perspective. This perspective pertains to the subjective feeling of being an acting and experiencing self with an outward perspective of the perceived world and an inward perspective

regarding oneself (Metzinger, 2003). The question of self-consciousness and self-referencing has occupied the minds of philosophers and psychologists for centuries. And recently, this topic has also been discussed in neuroscience (Northoff, et al., 2006). There is an emergent body of evidence in brain imaging research that a specific set of brain regions consisting of the medial prefrontal cortex (MPFC), posterior cingulate (PCC) in addition to midline parietal structures, lateral parietal regions, and medial and lateral temporal lobes is engaged during rest (Buckner, Andrews-Hanna, & Schacter, 2008; Gusnard & Raichle, 2001; Raichle, et al., 2001). There is substantial overlap between this default mode network (DMN) and the network involved in self-referential processes. For instance, activity in the DMN has been shown in tasks involving autobiographical memory retrieval (Andreasen, et al., 1995; Svoboda, McKinnon, & Levine, 2006) and mind wandering or spontaneous thoughts (Andrews-Hanna, Reidler, Huang, & Buckner, 2010; Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Mason, et al., 2007). This might not be surprising as a task-free condition such as resting-state allows individuals to think to themselves undisturbed.

Resting-state imaging studies can help to increase our knowledge of neural mechanisms underlying the phenomenal self-models in DID. On the other hand, research in DID can be of major value in comprehending self-referential processes in general by experimentally controlling and inducing dissociative parts (i.e., ANP and EP). In Experiment 2 described in chapter 5 (empirical part), we conducted a resting-state experiment with DID patients and actors mimicking DID.

3. Methods

3.1. Participants

The two experiments included in this present dissertation were carried out on the same samples of subjects. Fifteen female outpatients who met the DSM-IV (American Psychiatric Association, 1994) criteria for DID were enrolled in the study, and each DID patient was measured as ANP and EP. Therefore, a major inclusion criteria was the ability to alternate between ANP and EP at request and to remain activated, particularly as EP, for a substantial period of time in the scanner. Fifteen DID-simulating actors (matched in age and educational level with the DID group) were included as controls to test the claim that DID involves suggestion and role-playing. They were instructed and motivated to create an ANP and EP and to practice simulating these parts before the measurement. The instructions included a video showing a DID patient alternating between ANP and EP and detailed written information on the TSDP (Van der Hart, et al., 2006). Further details on the study sample will be discussed in the empirical part (chapter 5).

3.2. Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) is currently the most widely used method for studying neural processes in the human brain. The physical principles on which fMRI is based are complex, and a thorough discussion of them is beyond the scope of this thesis. Therefore, only the basic concepts will be briefly described. Functional MRI can be used to map activated brain regions. The fMRI signal constitutes an indirect measurement based on the strong relationship of neural activity and neurovascular properties (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). Two different techniques, which can be employed to assess diverse aspects of the haemodynamic response, will be discussed in the following.

3.2.1. The basics of blood-oxygenation-level dependent imaging

The blood-oxygenation-level dependent (BOLD) signal exploits the fact that oxygenated and deoxygenated blood have different magnetic properties (Pauling & Coryell, 1936; Thulborn, Waterton, Matthews, & Radda, 1982) -- oxygenated blood

($oHBO_2$) is paramagnetic, whereas deoxygenated blood ($dHBO_2$) is dimagnetic. When a brain region is neurally activated it consumes oxygen causing an initial decrease of oxyhemoglobin. After this initial dip (Malonek & Grinvald, 1996), the supply of oxygenated blood is higher as the actual need, which increases the ratio between oxygenated and deoxygenated blood (Fox & Raichle, 1986), and leads to a higher fMRI signal. In this context, deoxyhemoglobin can be considered as a form of endogenous tracer for measuring brain activity (Ogawa, Lee, Kay, & Tank, 1990). The temporal resolution of the BOLD signal in the range of sec is poor. The peak of the signal is reached approximately after 5 sec from stimulus onset and returns after 10 to 16 sec back to baseline. In contrast to the low temporal resolution, a good spatial resolution (approximately 2-3 mm) is achieved (Jäncke, 2005). The BOLD response ends with a post-stimulus undershoot. The mechanism of this undershoot is still unresolved (Van Zijl, Hua, & Lu, 2012). **Figure 1** depicts the time course of the BOLD signal change.

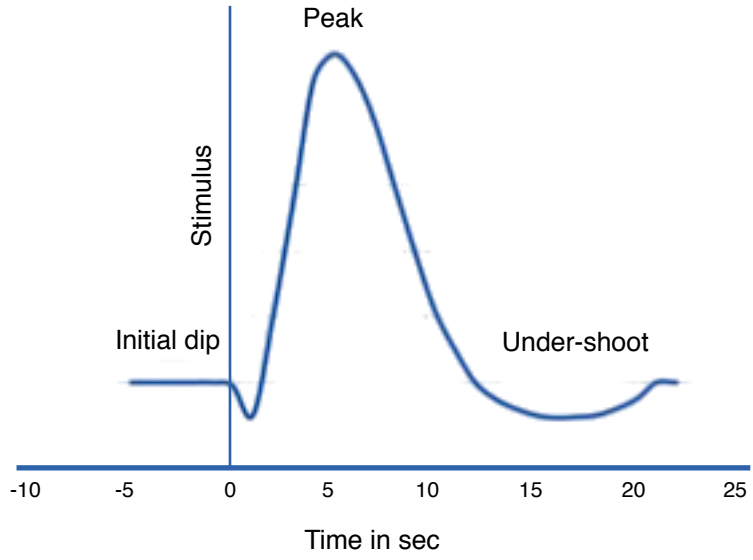


Figure 1. Time course of the BOLD signal.

3.2.2. Arterial spin labeling

With arterial spin labeling (ASL) perfusion MRI, brain perfusion can be noninvasively measured at rest and with task activation. This cerebral blood flow (CBF) reflects the volume of flow per unit brain mass per unit time and is expressed in physiological units of mL/g/min. In gray matter (GM), a typical value is roughly 60mL/100g/min

(Buxton, 2002). In ASL, arterial blood water is magnetically labeled using radiofrequency (RF) pulses. In contrast to CBF measurements in PET, no exposure to ionizing radiation is required (Detre, et al., 1994). The inverted spins in the blood water flow into the slice of interest in the brain, which leads to a reduction in total tissue magentization and, as a consequence, to a decline in the MR signal and image intensity. During this time, an image is taken (called the label image). To create another image (called control image), the experiment is then repeated without labeling the arterial blood. The label image and the control image are acquired in an interleaved fashion. Pairwise subtraction of label and control images yields a difference image, which has an intensity proportional to CBF (Wolf & Detre, 2007). **Figure 2** describes schematically this ASL acquisition procedure.

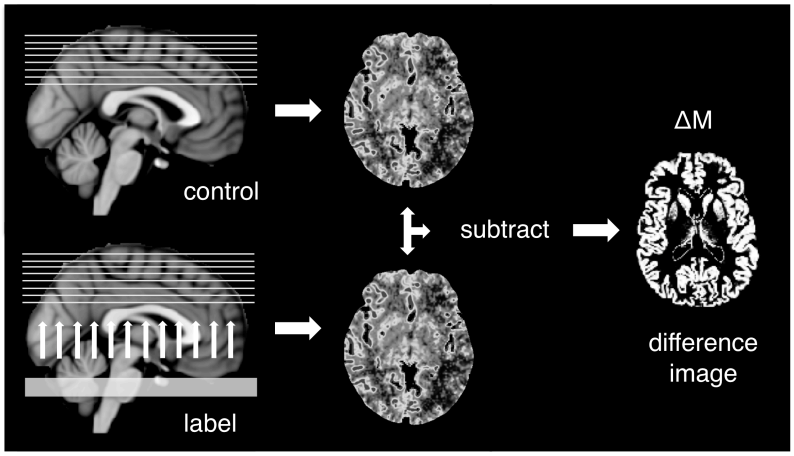


Figure 2. Basic concept of ASL perfusion MRI. Taking the difference of the control and label images yields an image (ΔM = M control – M label) that is proportional to CBF.

A mean perfusion CBF image is generated by averaging all difference images per subject. An example of such a CBF map is depicted in **Figure 3**.

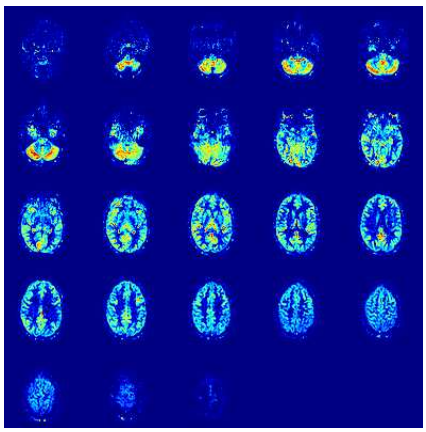


Figure 3. Example of a CBF map in 23 slices of a human brain (created in MATLAB, http://www.mathworks.ch/products/matlab). Color scale from blue to red indicates perfusion intensity.

Perfusion based fMRI has not received that much attention than imaging sequences based on the BOLD contrast. The main disadvantage of ASL compared to BOLD is the poor signal to noise ratio (SNR) of the ASL response -- typically less than half that of the BOLD response (Liu & Brown, 2007). The time between the labeling and image acquisition (i.e., delay time) is about one second corresponding to 1 mL of blood delivered to 100 mL of tissue (see above). This means that the inflowing blood magnetization constitutes only about 1% of the total signal, the rest being the tissue (Liu & Brown, 2007). In addition, the image coverage in ASL methods is inferior to that of BOLD with ASL studies typically acquiring a smaller number of slices and thicker slices compared to BOLD studies (Liu & Brown, 2007). Futhermore, the ASL effects are measured through comparison of label and control images, which means the temporal resolution is low because of the need to acquire two sets of images (Liu & Brown, 2007). Temporal resolution is further diminished by the time that is needed to let the labeled blood flow into the imaging region.

Nevertheless, ASL provides a variety of advantages compared to BOLD studies. BOLD signal changes are a result of an interaction between a number of physiological variables including CBF, cerebral blood volume (CBV), and oxygen utilization. Consequently, BOLD signal changes are expressed as a relative percentage signal change compared to a baseline, as they cannot be quantified in physiological units, and a change in the BOLD signal is not easy to interpret, as it can be related to age or disease that cause changes in any of these physiological variables (D'Esposito, Deouell, & Gazzaley, 2003). In contrast, ASL provides a

quantitative CBF measurement, and is therefore useful in the investigation of individual differences in brain metabolism. This is particularly beneficial for clinical neuroscience studies, as normal and patient populations can be compared in terms of an absolute quantitative perfusion measurement (Detre, Rao, Wang, Chen, & Wang, 2012). Furthermore, ASL is known to better reflect neural activity as compared to BOLD (Liu & Brown, 2007). The BOLD signal requires venous blood, which can contribute to activation-induced susceptibility changes, as it contains deoxyhemoglobin (Ogawa, et al., 1993). In contrast, the ASL perfusion signal is restricted to the capillary bed and, therefore, offers a measurement, which is well localized to the part of the vascular system where neural activity takes place (Liu & Brown, 2007). In addition, pairwise subtraction between adjacently acquired label and control images dramatically changes the noise of the ASL signal (i.e., baseline drifts, motion artefacts) compared to the BOLD signal (Wong, 1999; Zarahn, Aguirre, & D'Esposito, 1997). Independent studies have demonstrated that inter-subject and inter-session variability is decreased in ASL measures compared to BOLD (Aguirre, Detre, Zarahn, & Alsop, 2002; Tjandra, et al., 2005; Wang, et al., 2003). Moreover, the ability to use imaging sequences (e.g., spin-echo) that are insensitive to susceptibility effects reduce susceptibility-related signal losses (Liu & Brown, 2007).

Taken together, ASL methods are quantitative and stable over time and therefore most useful for longitudinal or multisite studies (Wolf & Detre, 2007).

3.3. Visual masking in functional magnetic resonance imaging

Masking can be used to manipulate perceptual awareness of visual stimuli. In backward masking, a target picture is shown briefly (i.e., subliminally) and is immediately followed by another masking stimulus to preclude conscious awareness of the target picture (Öhman, 2002; Wiens & Öhman, 2002). However, an aversively conditioned masked target can induce emotional reactions from subjects without being consciously perceived (Öhman & Soares, 1994). Therefore, backward masking is a powerful technique for studying preconscious (i.e., pre-attentive, automatic) processing of threatening stimuli in an fMRI setting.

In Experiment 1, backward masking was applied. The paradigm of this experiment will be described in detail in chapter 5 (empirical part), and only a short

overview is given in this section. Facial expressions are one of the most intensively studied objects in the emotion literature. We used neutral and angry faces from the Karolinska set (Karolinska Directed Emotional Faces (KDEF)) and included approximately half male and half female subjects (Lundquist, Flykt, & Öhman, 1998). Angry faces can be regarded as potent conditioned threat stimulus after sexual and physical abuse. Scrambled stimuli served as a baseline condition and were also presented subliminally (presentation time 16.7 msec). Black-and-white dotted masks immediately preceded and followed the subliminal stimuli and ensured that they could not be seen consciously. **Figure 4** depicts the stimulus material and a schematic representation of the masking paradigm. A beamer (digital light processing, DLP) projected the stimuli on a half-transparent screen, which could be seen via a mirror system placed on the head coil.

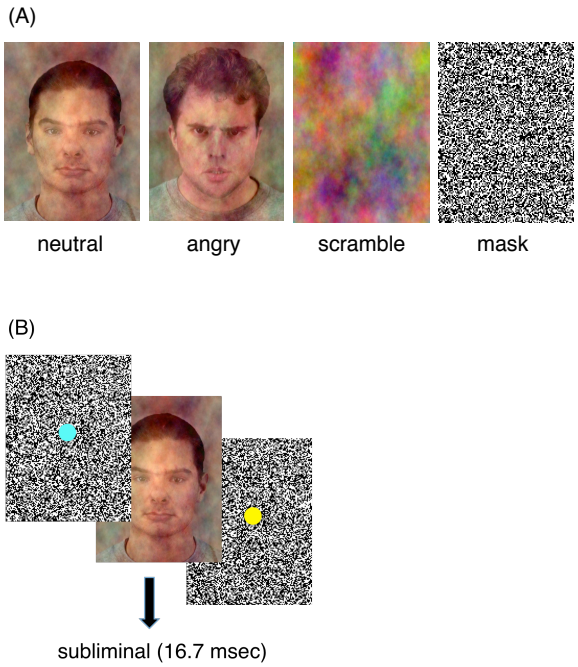


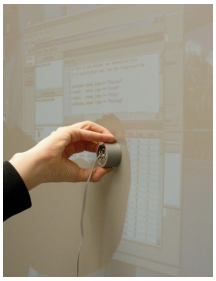
Figure 4. Experimental design. (A) Example stimuli (KDEF, identity number M12 and M30 (Lundquist, et al., 1998)) and visual noise mask. (B) Schematic representation of the masking paradigm.

Each mask contained a colored dot (yellow or turquoise). The color of the dot on the masks that preceded the experimental pictures was different from the color of the dot on the masks that followed these pictures. The participants were instructed to immediately press a button when they noticed that the color of the dot had changed. This button press task (based on Reinders, et al. (2005) and Reinders, Glascher, et

al. (2006)) was used to measure condition-dependent RTs. An attentional bias (AB) score was calculated by subtracting the mean value of the RTs related to scrambled stimuli from the mean value for the RTs related to neutral and related to angry faces, respectively. A positive AB score (i.e., longer RTs for facial stimuli than scrambled stimuli) can be interpreted as vigilance, and a negative one (i.e., longer RTs for scrambled stimuli than facial stimuli) as avoidance (Bakvis, et al., 2009; Putman, Hermans, & Van Honk, 2004; Van Honk, et al., 1998, 2000).

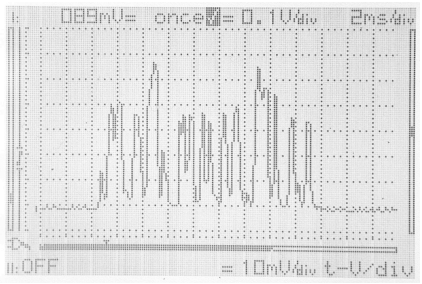
In masking paradigms, it is essential to check explicitly if the target pictures have been presented below the threshold of conscious awareness, and there are two general approaches to the valid measurement of the level of awareness (Cheesman & Merikle, 1984). The subjective approach employs a subjective report or “claimed unawareness” measure. Participants were as ANP and EP invited to report what they saw on the screen during the fMRI measurement. The objective approach defines unawareness in terms of performance on tasks that measure perceptual discrimination. We used a two-alternative forced-choice test. Following the fMRI measurement, a set of faces was presented masked again. After the subliminal presentation of each face, we supraliminally projected this target face together with a randomly chosen face matched in sex and emotional expression, and requested the participants to say or guess which of these two faces had been previously projected subliminally. If the mean of hits is approximately 50%, the level of detectability is at chance level (Kihlstrom, Barnhardt, & Tataryn, 1992), and it can be assumed that the participants had not consciously seen the experimental faces.

We also examined the projector’s capacity, using a light sensor, to project pictures subliminally (see **Figure 5**). The sensor was fixed on the screen while the computer was running a sequence of alternating black-and-white images with a presentation time of 16.7 msec. The sensor’s output was measured by a digital oscilloscope. The actual presentation time of the projector was around 16.5 msec ± 2 msec. It thus projected the subliminal pictures within the critical time limit.



light sensor

oscilloscope



output

Figure 5. Examination of the projector's capacity: Light sensor, oscilloscope, and the oscilloscope's output.

4. Aims and research questions

The principal purpose of the present work is to contribute to a better understanding of underlying neural mechanisms of DID. Psychobiological research of DID is particularly sparse, and the number of studies addressing DID is disproportionally low to the substantial prevalence rates in DID (see above) and subjective and economical costs associated with DID (Galbraith & Neubauer, 2000). The TSDP (Van der Hart, et al., 2006) provides testable hypotheses about dissociative reactions in response to various situations. In this context, prior studies investigating the neurophysiological underpinnings of DID might have failed to find significant differences between two dissociative parts, as they involved an ANP/ANP or EP/EP rather than an ANP/EP comparison (Coons, Milstein, & Marley, 1982; Hughes, Kuhlman, Fichtner, & Gruenfeld, 1990; Sar, Unal, Kiziltan, Kundakci, & Ozturk, 2001). This thesis focuses on the investigation of ANP and EP in DID patients as two prototypical dissociative parts of the personality.

Aims and research questions of Experiment 1: To assess preconscious processing of perceived threat in ANP and EP of DID patients and to compare these reaction patterns with actors who were instructed and motivated to simulate ANP and EP. The motivation for these aims is based on previous research demonstrating that ANP and EP in DID patients have different behavioral and psychobiological reactions to supraliminal and subliminal trauma-related cues and that controls instructed and motivated to simulate ANP and EP in DID were unable to mimic these reaction patterns (Hermans, et al., 2006; Reinders, et al., 2003; Reinders, Nijenhuis, et al., 2006; Reinders, et al., 2012).

In line with the TSDP (Van der Hart, et al., 2006) and the previous empirical findings, we hypothesized that ANP preconsciously mentally avoids neutral and angry masked faces, whereas EP is fixed in the faces. We speculated that the differences between ANP and EP are correlated with neural activity associated with disengagement and engagement in subliminal facial expressions and RTs indicating avoidance (i.e., negative AB score) and vigilance (i.e., positive AB score) of the involved faces. We also predicted that these differences are more pronounced

following angry compared to neutral faces. We furthermore hypothesized that actors have different behavioral and psychobiological reactions to the subliminal faces.

Aims and research questions of Experiment 2: To test the hypotheses that ANP and EP in DID patients have different perfusion patterns in response to rest instructions, and that perfusion is different in ANP and EP simulating actors. Previous studies (Hermans, et al., 2006; Reinders, et al., 2003; Reinders, Nijenhuis, et al., 2006) provided insights into dissociative part-dependent reactions to trauma-related stimuli. The present experiment extends the investigation to a task-free condition.

We hypothesized that in response to rest instructions, ANP and EP in DID have different patterns of brain perfusion and that comparisons of ANP and EP simulating controls yield different neural reactivity patterns than comparisons of ANP and EP in DID patients. We predicted that DID patients show relatively higher activation in areas which commonly exhibit increased neural activity following rest instructions (default mode activity), and that controls elicit a brain pattern distinct from the default mode activity because simulating an ANP and EP and being a genuine ANP and EP constitute different mental states.

5. Empirical part

5.1. Experiment 1: Backward masking paradigm

Dissociative part-dependent biopsychosocial reactions to backward masked angry and neutral faces: An fMRI study of dissociative identity disorder

Published in NeuroImage: Clinical 3 (2013) 54-64

Authors:
Yolanda R. Schlumpf, MSc[a], Ellert R.S. Nijenhuis, PhD[b], Sima Chalavi, MSc[c], Ekaterina V. Weder, MSc[d], Eva Zimmermann, MSc[e], Roger Luechinger, PhD[f], Roberto La Marca, PhD[g], A.A.T. Simone Reinders, PhD[c,h], Lutz Jäncke, PhD[a,i]

a Division of Neuropsychology, Institute of Psychology, University of Zurich, Switzerland
b Top Referent Trauma Center Mental Health Care Drenthe, Assen, The Netherlands
c Department of Neuroscience, University Medical Center Groningen, and BCN Neuroimaging Center, University of Groningen, Groningen, The Netherlands
d Private practice, Eschen, Liechtenstein
e Fribourg General Hospital, Fribourg, Switzerland
f Institute for Biomedical Engineering, University and ETH Zurich, Switzerland
g Division Clinical Psychology and Psychotherapy, Institute of Psychology, University of Zurich, Switzerland
h Department of Psychosis Studies, Institute of Psychiatry, King's College London, London, United Kingdom
i International Normal Aging and Plasticity Imaging Center, University of Zurich, Switzerland

Keywords: dissociative identity disorder, neuroimaging, backward masking, face perception, emotional ambiguity, hypervigilance

Acknowledgments: This research was supported by the Forschungskredit of the University of Zurich. A.A.T.Simone Reinders is supported by the Netherlands Organization for Scientific Research (www.nwo.nl), NWO-VENI grant no. 451-07-009. We would like to thank the colleagues of Prof. Jäncke's lab for their helpful comments

and Franz Liem and Thomas Reber for their technical support. Special thanks go to the patients and their therapists for participating in the study.

5.1.1. Abstract

Objective: The Theory of Structural Dissociation of the Personality (TSDP) proposes that dissociative identity disorder (DID) patients are fixed in traumatic memories as “Emotional Parts” (EP), but mentally avoid these as “Apparently Normal Parts” of the personality (ANP). We tested the hypotheses that ANP and EP have different biopsychosocial reactions to subliminally presented angry and neutral faces, and that actors instructed and motivated to simulate ANP and EP react differently.

Methods: Women with DID and matched healthy female actors (CON) were as ANP and EP (DIDanp, DIDep, CONanp, CONep) consecutively exposed to masked neutral and angry faces. Their brain activation was monitored using functional magnetic resonance imaging. The black-and-white dotted masks preceding and following the faces each had a centered colored dot, but in a different color. Participants were instructed to immediately press a button after a perceived color change. State anxiety was assessed after each run using the STAI-S. Final statistical analyses were conducted on 11 DID patients and 15 controls for differences in neural activity, and 13 DID patients and 15 controls for differences in behavior and psychometric measures.

Results: Differences between ANP and EP in DID patients and between DID and CON in the two dissociative parts of the personality were generally larger for neutral than for angry faces. The longest reaction times (RTs) existed for DIDep when exposed to neutral faces. Compared to DIDanp, DIDep was associated with more activation of the parahippocampal gyrus. Following neutral faces and compared to CONep, DIDep had more activation in the brainstem, face-sensitive regions, and motor-related areas. DIDanp showed a decreased activity all over the brain in the neutral and angry face condition. There were neither significant within differences nor significant between group differences in state anxiety. CON was not able to simulate genuine ANP and EP biopsychosocially.

Conclusions: DID patients have dissociative part-dependent biopsychosocial reactions to masked neutral and angry faces. As EP, they are overactivated, and as ANP underactivated. The findings support TSDP. Major clinical implications are discussed.

5.1.2. Introduction

Dissociative Identity Disorder (DID) is the most complex of dissociative disorders (American Psychiatric Association, 1994). According to the Theory of Structural Dissociation of the Personality (TSDP) (Nijenhuis, et al., 2002; Van der Hart, et al., 2006), DID is a severe form of posttraumatic stress disorder (PTSD) encompassing different types of dissociative parts of the personality. In TSDP, personality is understood as a whole biopsychosocial system, and dissociative parts as subsystems of this whole system. Van der Hart et al. (2006) propose a distinction between “Emotional Parts” (EP) and “Apparently Normal Parts” (ANP) of the personality. DID involves more than one EP and more than one ANP. Switching between these dissociative parts is a major characteristic of DID. EP is fixed in traumatic memories. As ANP, DID patients may claim a degree of amnesia for these memories, do not or not sufficiently personify traumatic experiences and memories, and attempt to mentally avoid trauma-related stimuli. TSDP distinguishes different prototypical subtypes of EP (Nijenhuis & Den Boer, 2009). Some subtypes show strong emotional reactions to trauma-related stimuli and engage in active mammalian defensive reactions (e.g., freeze, flight, attachment cry), whereas another subtype engages in passive mammalian defense (playing dead), which implies emotional and bodily anesthesia.

Severe and chronic dissociative symptoms tend to develop in the context of severe and chronic childhood traumatization, which includes profound attachment disruptions (Dalenberg, et al., 2012; Diseth, 2006; Nijenhuis & Den Boer, 2009; Nijenhuis, et al., 2002; Ogawa, et al., 1997; Trickett, et al., 2011). In a Positron Emission Tomography (PET) study, female DID patients listened as ANP and as EP (in Reinders, Nijenhuis, et al. (2006) referred to as a neutral identity state (NIS) and trauma-related identity state (TIS)) to autobiographical neutral and trauma scripts while their psychophysiological and brain activation was monitored (Reinders, et al., 2003; Reinders, Nijenhuis, et al., 2006). As ANP, the patients in this study reacted similarly to the neutral and the trauma memory scripts. This finding suggests low emotional involvement in trauma-related stimuli, which is consistent with TSDP. In this study, EP (subtype active defense), as compared to the ANP, showed significant activation of many areas also observed in PTSD patients while being confronted with a personalized trauma script (Lanius, et al., 2001; Rauch, et al., 1996; Shin, et al.,

2001). EP but not ANP demonstrated strong psychophysiological reactions to the trauma script. Thus, EP but not ANP was psychobiologically aroused. ANP showed a brain activation pattern similar to patients with depersonalization disorder (Simeon, et al., 2000) and PTSD patients with negative dissociative symptoms to trauma-related stimuli (Lanius, Bluhm, Lanius, & Pain, 2006; Lanius, et al., 2002).

According to the sociocognitive view (also referred to as fantasy model (Dalenberg, et al., 2012)), DID is caused by high fantasy proneness, role-playing, suggestibility, and iatrogenic suggestion (Giesbrecht, et al., 2008; Lilienfeld, et al., 1999; Merckelbach, Devilly, & Rassin, 2002; Merckelbach & Muris, 2001; Merskey, 1992; Spanos, 1994). Few suggestions would suffice to generate dissociative parts in suggestible, fantasy prone individuals (Spanos, 1996). However, a recent symptom provocation functional brain imaging study provided evidence suggesting that DID is not linked to fantasy proneness. Reinders et al. (2012) found that neither high nor low fantasy prone mentally healthy women instructed and motivated to simulate ANP and EP were able to enact the psychophysiological and neural activation patterns of the genuine ANP and EP.

A study by Hermans et al. (2006) used backward masking to expose DID patients to angry and neutral faces for 25 msec. Attentional bias scores were calculated by subtracting the reaction times (RTs) needed to color-name the mask that immediately followed a neutral face from the RTs needed to color-name the mask that immediately followed an angry face. A positive attentional bias score (i.e., longer RT for angry than neutral faces) was interpreted as vigilance, and a negative one (i.e., longer RT for neutral than angry faces) as avoidance (Bakvis, et al., 2009; Putman, et al., 2004; Van Honk, et al., 1998, 2000). Hermans et al. (2006) found that as ANP but not as EP, DID patients had a negative attentional bias in that their RT to angry faces was faster than that to neutral faces. Healthy controls instructed and motivated to role-play ANP and EP did not show this negative bias. Taken together, these behavioral data also contradict the sociocognitive view of DID.

The findings from Reinders et al. (2003, 2012), Reinders, Nijenhuis et al. (2006), and Hermans et al. (2006) support the hypotheses derived from TSDP that as EP engaging in active defense, DID patients are fixed in traumatic memories and demonstrate unusually strong cortical, subcortical and vegetative reactions (i.e., hyperarousal) to reminders of traumatic experiences. As ANP on the other hand, they

react to trauma-related cues in a depersonalized and detached manner (i.e., hypoarousal). In addition, these differences between ANP and EP exist already at a preconscious level, that is, with respect to pre-attentive reactivity to external and internal stimuli.

EP's preconscious fixation on perceived threat (Hermans, et al., 2006) is hypothesized to be associated with neural networks related to perceptual and emotional processing of the angry faces. Reactions to emotional faces compared to neutral faces are expected to be associated with greater activation in early visual areas (striate cortex) and higher order visual areas (extrastriate cortex) including face-sensitive regions in the fusiform gyrus (Vuilleumier & Pourtois, 2007). Functional imaging studies have identified additional areas in the extrastriate occipito-temporal region involved in the visual analysis of faces (i.e., lateral inferior occipital cortex, sulcus temporalis superior [STS]) (Haxby, Hoffman, & Gobbini, 2000). Amaral and colleagues have demonstrated that enhanced activity within the visual cortex as reaction to emotional stimuli is mainly driven by the amygdala, which has strong anatomical connections to visual areas (Amaral, Price, Pitkanen, & Carmichael, 1992). One of the main contributions of the amygdala is to support rapid reaction to potential or actual sources of danger (Davis & Whalen, 2001; LeDoux, 1998; Phan, Wager, Taylor, & Liberzon, 2002). Activity within the amygdala can occur even if the threatening stimuli are presented below the level of awareness (Morris, Ohman, & Dolan, 1998; Whalen, et al., 1998). Amygdala responsitivity and associated vigilance are abnormally enhanced in PTSD (Armony, et al., 2005; Rauch, et al., 2000; Shin, et al., 2004). This hypervigilance fits clinical observations that as EP engaged in active defense, patients are continuously scanning the environment for threat cues. Engagement in active defense may thus be associated with enhanced activation in motor-related areas, which was found in the study of Reinders, Nijenhuis et al. (2006) as well (i.e., basal ganglia, cerebellum). This proposal also fits the observations that the cortical motor system is activated during emotional processing in humans (Hajcak, et al., 2007; Oliveri, et al., 2003), which prepares the individual for an appropriate motor reaction (Baumgartner, Willi, & Jancke, 2007).

In most previous functional imaging studies with masked stimuli investigating PTSD patients, the analysis was mainly restricted to the amygdala as a key brain structure for emotional processing (Armony, et al., 2005; Hendler, et al., 2003;

Rauch, et al., 2000). This focus on the amygdala reflected a particular a priori interest in the role of this brain structure in fear. However, Sakamoto and colleagues conducted a whole-brain analysis (Sakamoto, et al., 2005). In this study, PTSD patients showed significantly higher activations to masked traumatic images in the left parahippocampal gyrus and the tail of the left hippocampus.

Per definition neutral faces do not express a clear emotion, thus can be perceived as emotionally ambiguous. Like anxiety disorder patients, and consistent with clinical observations, as EP, DID patients may have difficulty tolerating uncertainty or ambiguity (Grillon, et al., 2008; Holaway, Heimberg, & Coles, 2006) and may tend to interpret ambiguous stimuli in negative ways (Bishop, 2007; Eysenck, Mogg, May, Richards, & Mathews, 1991).

The current functional magnetic resonance imaging (fMRI) study aims to examine the underlying neural activation patterns involved in ANP-dependent and EP-dependent preconscious reactivity. Based on the mentioned theoretical and empirical grounds, we specifically hypothesized that compared to (i) ANP in DID patients, and (ii) EP in controls, EP in DID patients have a different pattern of neural activity in response to subliminally presented faces, particularly more activity in primary and higher-order visual areas, face-sensitive areas including extrastriate occipito-temporal regions, limbic structures including the amygdala and hippocampal/parahippocampal region, and motor-related areas comprising the cortical motor system, basal ganglia, and cerebellum. We also hypothesized that (iii) these differences are more pronounced following angry faces, that (iv) EP in DID patients have longer RTs to these faces than ANP in DID patients and than EP in controls, and that (v) comparisons of ANP and EP in controls yield different neural and behavioral reactivity patterns than comparisons of ANP and EP in DID patients.

5.1.3. Methods and materials

Participants

Fifteen female outpatients who met the DSM-IV American Psychiatric Association (American Psychiatric Association, 1994) criteria for DID were enrolled in the study. They were recruited from private practitioners of psychiatry and psychotherapy and psychiatric outpatient departments in Switzerland and Germany. The clinical diagnosis was independently checked by clinical experts in dissociative disorders (E. Weder [EW] and E. Zimmermann [EZ]) using the German version of the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D) (Steinberg, 1993), the (SKID-D) (Gast, Hofmann, Oswald, & Zündorf, 2000). All patients had to be involved in a treatment phase involving exposure to trauma-related memories (Steele, Van der Hart, & Nijenhuis, 2005; Van der Hart, et al., 2006). Exclusion criteria were comorbid psychosis, drug abuse or addiction, antisocial or histrionic personality disorder, and a neurological or organic brain disease. Two patients were free of medication. All other patients were medicated predominantly with antidepressant medication.

Fifteen female actors who were motivated to simulate ANP and EP served as controls. They did not differ significantly from the patients in age (controls: M=43.2 years, SD=10.4; patients: M=43.3 years, SD=9.1; $t(28)=0.019$, $p>.05$) and educational level (controls: M=4.7, SD=1.2; patients: M=4.1, SD=1.5; $t(26.099)=-1.341$, $p>.05$; the educational level was assessed by a 7-point Likert scale based on the common European educational system). The controls were interviewed by EW and EZ using the SKID-D (Gast, et al., 2000). They also completed the German version of the Posttraumatic Diagnostic Scale (PDS) (Ehlers, Steil, Winter, & Foa, 1996) and the Beck Depression Inventory II (BDI-II) (Hautzinger, Keller, & Kühner, 2006) to ensure that none of the controls had a dissociative disorder, PTSD, and/or major depression. The actors watched a video showing a DID patient talking to her therapist. In the video, the therapist invites the patient to alternate between ANP and EP. Based on detailed written information on TSDP (Van der Hart, et al., 2006), the actors were instructed and motivated to create an ANP and EP using a list of properties (e.g., name, sex, age). ANP should be a dissociative part without personalized memories of traumatizing events and EP as a dissociative part with personalized traumatic memories. The actors were requested to practice simulating

ANP and EP as often as they deemed necessary to adequately enact these roles but at least three times before the MRI measurement. Patients completed as ANP and EP the State Anxiety Inventory (STAI-S) (Laux, Glanzmann, Schaffner, & Spielberger, 1981) immediately after the fMRI measurement, as did the controls to check if the actors had understood and followed the instructions to simulate an ANP and EP.

Each subject was informed about risks and inconveniences associated with the experiment before written informed consent was obtained. All procedures were approved by the local ethical committee and were conducted in accordance with the standards set by the Declaration of Helsinki. All participants received a financial compensation of 80 Swiss Francs for their participation.

Stimuli and experimental design

A backward masking paradigm was used to investigate preconscious mental reactivity to masked faces. The Karolinska Directed Emotional Faces (KDEF) served as photographic stimuli. They involved neutral, happy, fearful, and angry facial expressions, including approximately half male and half female subjects (Lundquist, et al., 1998). The selection of the facial pictures used in the study was based on a rating of the intensity and genuineness of the displayed emotions (Van Balen, 2005). In addition to the faces, houses and scrambled images were presented. Scrambled stimuli were created in Fourier space by setting a low level of phase-coherence (Reinders, Den Boer, & Buchel, 2005; Reinders, Glascher, et al., 2006) in face pictures and served as baseline stimuli. All pictures were matched for luminance, contrast, brightness, and spatial frequency information (Rainer, Augath, Trinath, & Logothetis, 2001; Reinders, et al., 2005; Reinders, Glascher, et al., 2006).

The pictures were generated by the software Presentation (version 14.1, http://www.neurobs.com) on a computer (Intel Core 2 Duo CPK, 60-Hz refresh rate) outside the scanner room. A DLP beamer (Plus U2-1110) projected them on a half-transparent screen, which could be seen via a mirror system placed on the head coil. All blocks of pictures were shown three times in a pseudorandomized order (18 blocks in total). Order effects were controlled by using two playlists (P1, P2), which were randomly assigned to ANP and EP. Each block consisted of 10 subliminal

pictures (16.7 msec) and 11 black-and-white dotted masks (2.5 sec). The masks, also used in previous studies (Henke, Mondadori, et al., 2003; Henke, Treyer, et al., 2003), immediately preceded and followed the subliminal stimuli. This procedure ensured that the pictures could not be consciously perceived. The duration of the mask (equivalent to the interstimulus interval) was jittered by ± 1 sec in randomized steps of 0.5 sec. Every block lasted for 27.5 sec and was separated by a 2.5 sec mask (interblock interval), resulting in a total time of 9 min per run. **Figure 6** depicts the temporal sequence of events in a block.

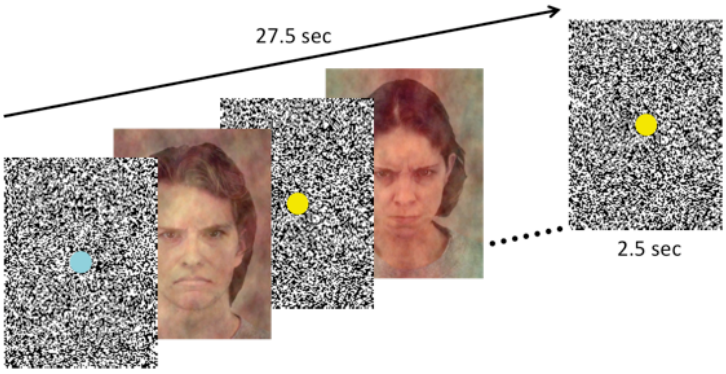


Figure 6. Experimental design. Example stimuli (KDEF, identity number M14 and F20 (Lundquist, et al., 1998)), masks, and fixation dots are presented from one block displayed during the fMRI measurement.

A button press task (based on Reinders, et al. (2005) and Reinders, Glascher, et al. (2006)) was used to measure condition-dependent RTs. Each mask contained a colored dot (yellow or turquoise). The color of the dot on the masks that preceded the experimental pictures was different from the color of the dot on the masks that followed these pictures. The participants were instructed to immediately press a button when they noticed that the color of the dot had changed. To direct the participants' gaze to the center of the faces, the dots on the masks were positioned at the place that corresponded with the center between the eyebrows of the faces. Each participant was first tested as ANP, and then as EP. The patient switched between dissociative parts of the personality outside the scanner room with little guidance from the research clinician. Inadvertent switches to a different dissociative part than the intended ANP or EP during the fMRI measurement were checked by asking the participants after the run what dissociative part had been present during

the run. If there had been a switch to or a co-activation of an unintended dissociative part, the run was repeated, which was the case in one ANP and two EPs. A LED light of the response box in the scanner room switched on and off in synchrony with the participants' button presses. The authors observed that irregular flashing of this light was a good indicator of co-awareness of and/or switching to an unintended dissociative part during the experiment in DID patients. DID patients behaving like this explained that they had major difficulty to execute the button press task in an adequate fashion. For example, they reported that an unintended dissociative part wanted to participate in the task but was not or not fully aware of task instructions. Therefore, the authors closely watched the regularity of the LED flashing. It appeared that DID patients with irregular patterns of button presses were precisely the patients who were removed from the statistical analysis for other methodological reasons (see later).

Determination of awareness

The level of awareness of the masked images was determined at the very end of the experiment, outside of the scanner, using a subjective and an objective test (Cheesman & Merikle, 1984). The subjective test involves the participant's self report. Thus, the ANPs and EPs were asked what they had seen while lying in the scanner. The objective test is a forced-choice task, and constitutes the 'gold-standard' for the determination of awareness (Cheesman & Merikle, 1984; Greenwald, Draine, & Abrams, 1996; Holender, 1986). The subjective and objective tests demonstrated that the participants had not consciously seen the experimental images (see **Supplementary Findings 1** and **Supplementary Table 1**). A light sensor (Vishay Semiconductors) was used to examine the beamer's capacity to project pictures within the refresh rate of the computer's graphic card (NVIDIA Quadro FX 1700, 60-Hz) (see **Supplementary Findings 2**).

Image acquisition and data preprocessing

Functional magnetic resonance imaging (fMRI) scanning was performed at the University Hospital of Zurich with a 3-T Philips Achieva whole-body magnetic

resonance imaging equipped with an eight-channel Philips SENSE head coil. A total of 325 T2*-weighted echo planar image volumes, with blood-oxygen-level-dependent (BOLD) contrast (imaging parameter: echo time=30msec, repetition time=1.7sec, flip-angle=79º, FOV=220x220x107mm, slice thickness=2.4mm, slice gap=1mm, acquired voxel size=2.75x2.75x2.4mm, slices per volume=32, SENSE factor=2), were acquired during a single run. Initial 'dummy' volumes were obtained to ensure BOLD saturation. The data analysis was performed with the parametric mapping software SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Standard imaging pre-processing and statistical analysis procedures were applied. To account for movement artifacts, the functional images were realigned to the mean volume and coregistered onto the subject specific T1 image. This T1 image was normalized using the unified segmentation approach (Ashburner & Friston, 2005). The resulting normalization matrix was applied to the functional volumes, which transformed them into MNI space (new voxel size=2x2x2mm). Data were spatially smoothed with an 8-mm full width at half-maximum (FWHM) Gaussian kernel. In line with the experimental design, the BOLD data was modeled with a block design convolved with the standardized canonical haemodynamic response function (HRF). In one ANP of a DID patient, we observed huge imaging artifacts. One ANP of a DID patient reported that she had fallen asleep during the measurement. For one patient's EP, we found massive movement artifacts and one patient's EP was unable to complete the measurement. In view of our repeated measures ANOVA, the data of these four patients were omitted casewise. The final brain imaging statistical analysis was performed with data of 11 participants in the patient group and 15 in the control group.

A model with six condition and six movement regressors (with the realignment parameters) was aligned for each participant for ANP and EP separately at the first level analysis. The current analyses are restricted to the contrasts Neutral-Scramble (N-S) and Angry-Scramble (A-S). The results of the other contrasts will be published elsewhere. At the second level, the data were analyzed using a factorial design that consisted of two independent variables resulting in a 2×4 ANOVA with repeated measures on the second factor: Group (two levels: DID/CON), Condition (four levels: ANP N-S/ANP A-S/EP N-S/EP A-S). The analysis was based on a whole-brain voxel-wise comparison. For the main effect of condition, main effect of group, and interaction effect, we employed an uncorrected statistical threshold (i.e., voxel level of

significance uncorrected [unc.] for multiple testing for the whole brain) of p<.001 with respect to our a priori defined regions. The selection of these regions is based on previous studies outlined in the introduction section (Hajcak, et al., 2007; Haxby, et al., 2000; Reinders, Nijenhuis, et al., 2006; Sakamoto, et al., 2005; Vuilleumier & Pourtois, 2007; Whalen, et al., 1998). To avoid type-2 errors, statistical thresholds of similar sizes have been used in affective and clinical neuroscience research (Felmingham, et al., 2008; Phelps, et al., 2001). Where no a priori hypothesis was available, we only accepted brain areas that reached a corrected p-value (p<.05). Corrected p-values are reported based on the family-wise error (FWE) correction at cluster level (Friston, Holmes, Poline, Price, & Frith, 1996; Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994).

The participants were measured as ANP and EP in the patient group (DIDanp/DIDep) and in the control group (CONanp/CONep). The following eight planned comparisons were performed: DIDanp-DIDep N-S, CONanp-CONep N-S, DIDanp-CONanp N-S, DIDep-CONep N-S, DIDanp-DIDep A-S, CONanp-CONep A-S, DIDanp-CONanp A-S, DIDep-CONep A-S. Planned comparisons were not orthogonal. Statistical thresholds for a priori defined regions for these planned comparisons were adjusted for multiple testing using Bonferroni correction (p<.05/8= p<.000125). All tests were one-sided, thus, were performed twice to assess positive differences in the BOLD signal in one and in the inverse contrast. Again, where no a priori hypothesis was available, we only accepted brain areas that survived FWE correction at cluster-level (p<.05). A cluster-size threshold of 7 voxels was applied. Only the first peak of a cluster and only the most significant finding of a brain area are reported in the **Table 2** to **5**. The exact location of all clusters was defined using the Harvard-Oxford cortical and subcortical structural atlases (Desikan, et al., 2006) and by visual inspection on a high-resolution T1-weighted image in FSL (http://www.fmrib.ox.ac.uk/fsl). The cingulate subregions were named according to Vogt's cytoarchitectonic division (Vogt, 2005).

Data analysis: behavioral reactions

An attentional bias (AB) score was calculated by subtracting the mean value of the RTs for the three scrambled face blocks (S) from the mean value for the RTs of the

three neutral face blocks (N) and the angry face blocks (A), respectively. The data of the participant who fell asleep and the one whose EP was not able to finish the measurement were excluded. The final statistical analysis was performed with data of 13 participants in the patient group and 15 in the control group. We calculated a 2×4 ANOVA with repeated measures on the second factor: Group (two levels: DID/CON), Condition (four levels: ANP N-S/ANP A-S/EP N-S/EP A-S) in SPSS18. For the main effect of condition, main effect of group, and interaction effect, p-values were set at .05. The following eight planned comparisons were performed: DIDanp-DIDep N-S, CONanp-CONep N-S, DIDanp-CONanp N-S, DIDep-CONep N-S, DIDanp-DIDep A-S, CONanp-CONep A-S, DIDanp-CONanp A-S, DIDep-CONep A-S. Planned comparisons were not orthogonal. Therefore, Bonferroni correction was applied and p-values were set at .00625, one-tailed.

Furthermore, the following four post-hoc t-tests were calculated to ensure that a RT difference can be explained by a face-specific effect: DIDanp N-S versus DIDanp A-S, DIDep N-S versus DIDep A-S, CONanp N-S versus CONanp A-S, CONep N-S versus CONep A-S. Bonferroni adjusted p-values were set at .0125, one-tailed.

Data analysis: state anxiety

A total value of the STAI-S (sum of obtained scores in the questionnaire) was calculated for each participant. The data of the participant who fell asleep and the one whose EP was not able to finish the measurement were excluded. The final statistical analysis was performed with data of 13 participants in the patient and 15 in the control group.

We calculated a 2×2 ANOVA with repeated measures on the second factor: Group (two levels: DID/CON), Type of dissociative part (two levels: ANP/EP) in SPSS18. For the main effect of group, main effect of type of dissociative part, and interaction effect p-values were set at .05.

5.1.4. Results

Behavioral data

There was a significant interaction effect of group by condition ($F(1,26)=4.82$, $p<.05$, partial $h^2=.16$). The main effect of group and the main effect of condition did not reach a significant threshold ($p>.05$). In AB N-S, Bonferroni corrected planned comparisons revealed a RT difference between DIDanp and DIDep ($t(12)=-3.15$, $p<.00625$, $d=1.31$). In AB A-S, planned comparisons did not reveal any significant results ($p>.00625$). Nevertheless, there is a clear positive AB N-S and a tendency to a positive AB A-S in DIDep (**Figure 7**).

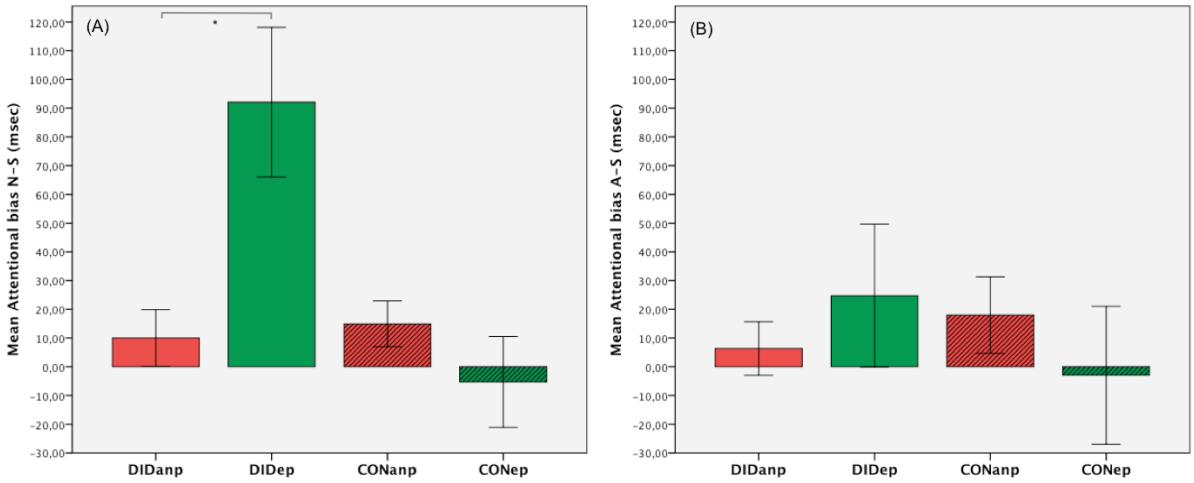


Figure 7. Mean attentional bias (AB) score (reaction times [RTs] for emotional faces minus RTs for scrambled faces) for (A) the neutral faces (AB N-S) and (B) the angry faces (AB A-S) in msec (±SEM). A positive AB indicates vigilance, a negative AB indicates avoidance, * $p<.00625$ (Bonferroni corrected).

We observed a significantly longer RT in DIDep N-S compared to DIDep A-S ($t(12)=2.69$, $p<.0125$, $d=0.73$). All other post-hoc tests did not reach the critical threshold ($p>.0125$). **Figure 8** depicts the mean and standard error of RT (A-S) – (N-S) in DIDanp, DIDep, CONanp, and CONep.

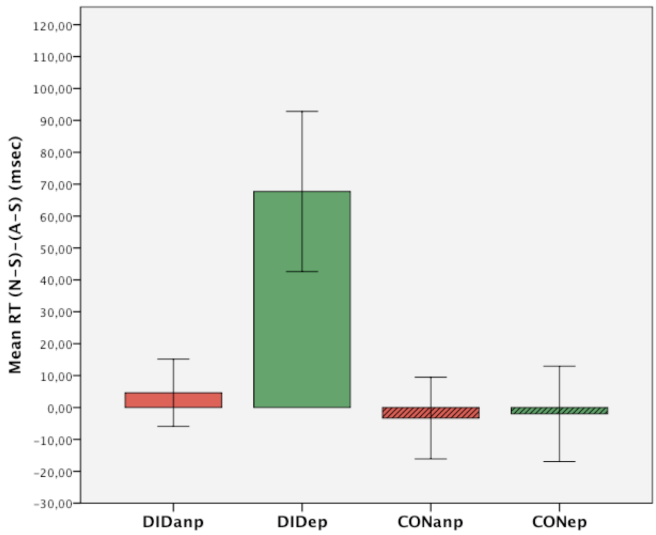


Figure 8. Mean reaction time (N-S)-(A-S) of ANP and EP in DID and CON (±SEM).

State anxiety

There was neither a significant main effect of group, nor a significant main effect of type of dissociative part, nor an interaction effect of group by type of dissociative part (p>.05). **Table 1** summarizes the descriptive statistics of the STAI-S score in DIDanp, DIDep, CONanp, and CONep.

Table 1. Descriptive statistics of state anxiety

STAI-S	Mean	SD
DID (n=13)		
DIDanp	49.92	11.64
DIDep	52.90	14.83
CON (n=15)		
CONanp	48.87	13.22
CONep	49.80	10.15

Note. STAI-S, state anxiety inventory; DIDanp, ANP DID group; DIDep, EP DID group; CONanp, ANP control group; CONep, EP control group

Neural data

Repeated measures ANOVA

We found a significant main effect of condition (putamen, posterior part of the parahippocampal gyrus) and a significant interaction effect of group by condition (parahippocampal gyrus, middle temporal gyrus) (**Table 2**). There was no significant main effect of group.

Table 2. Main effect condition and interaction effect

			MNI coordinates[a]				
	Brain area	Side	*x*	*y*	*z*	k*E*	*F* value
Main effect condition	Putamen	L	-24	6	0	73	8.70
	Parahippocampal gyrus (posterior part)	R	18	-36	-10	33	7.90
Interaction effect	Parahippocampal gyrus (anterior part)	R	16	-10	-24	29	9.60
	Middle temporal gyrus[b]	R	62	-38	-8	17	7.31

Note. R/L, left or right hemisphere; k*E*, cluster-size in voxels (one voxel is 2x2x2mm)
[a] MNI coordinates (in mm) refer to the maximum of signal change in each region
[b] ventral bank of the sulcus temporalis superior

Planned comparisons

Within-group comparisons of two different types of dissociative parts of the personality (i.e., ANP-EP comparisons) are listed in **Table 3**. ANP-EP comparisons between groups are given in **Table 4** and **5**.

Within-group ANP-EP comparisons

In the angry and neutral face condition, DIDep had more activation in the parahippocampal gyrus than DIDanp (DIDep-DIDanp N-S/A-S, **Table 3**). This activation was not found for ANP versus EP in controls. The neutral faces but not the angry faces evoked a significantly increased right amygdala activity as well as in several cortical regions in CONanp compared to CONep (CONanp-CONep N-S, **Table 3**).

Table 3. ANP/EP effects within groups in response to masked angry and neutral faces as compared to scrambled faces (A-S, N-S)

			MNI coordinates[a]				
Condition A-S	Brain area	Side	*x*	*y*	*z*	k*E*	*T* value
DIDanp - DIDep	n.s						
DIDep - DIDanp	Parahippocampal gyrus (anterior part)	R	20	-14	-26	9	4.20
CONanp - CONep	n.s.						
CONep – CONanp	n.s						
Condition N-S							
DIDanp - DIDep	n.s						
DIDep - DIDanp	Parahippocampal gyrus (anterior part)	R	16	-12	-26	11	4.27
CONanp - CONep	Superior frontal gyrus	L	-20	28	54	140	4.94*
	aMCC/pMCC	R	2	12	36	277	4.65*
	Precentral gyrus (premotor cortex)	L	-42	-4	46	25	4.26
	Amygdala	R	26	-6	-22	16	4.15
	Middle temporal gyrus (temporooccipital part)	R	58	-56	2	7	4.03
CONep – CONanp	n.s.						

Note. R/L, left or right hemisphere; k*E*, cluster-size in voxels (one voxel is 2x2x2mm); n.s., not significant; DIDanp, ANP DID group; DIDep, EP DID group; CONanp, ANP control group; CONep, EP control group; aMCC, anterior midcingulate cortex; pMCC, posterior midcingulate cortex
[a] MNI coordinates (in mm) refer to the maximum of signal change in each region
* corrected for multiple comparisons using cluster-level statistics, $p < .05$

Between-group ANP-EP comparisons

In the angry face condition and compared to CONep, DIDep was associated with more activation in the precentral gyrus (DIDep-CONep A-S, **Table 4**). In the neutral face condition (DIDep-CONep N-S, **Table 4**), the same contrast demonstrated increased neural activation for DIDep. Multiple large clusters reached our predefined statistical thresholds. The first cluster with a peak value in the left dorsal brainstem includes several mainly left lateralized areas in the occipito-temporal junction (lingual gyrus, temporal occipital fusiform gyrus, and occipital fusiform gyrus) and the left parahippocampal gyrus (**Figure 9**). Within this cluster, brainstem and lingual gyrus survived FWE correction for whole-brain multiple comparisons (p<.05, **Table 5**). DIDep had more activation in several a priori defined regions (middle temporal gyrus,

STS, lateral occipital cortex, occipital pole). As this type of dissociative part, DID patients also had more activation in several motor-related areas (pre-supplementary motor area, precentral gyrus).

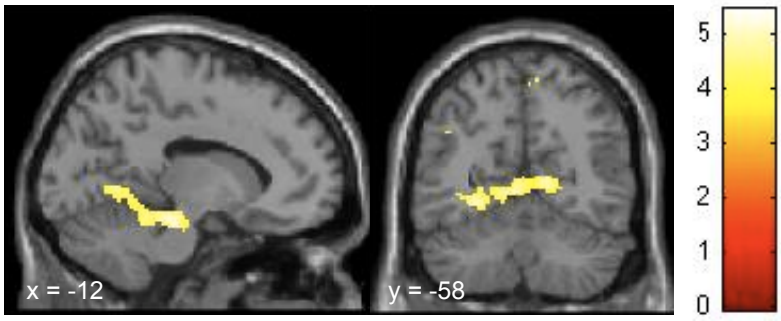


Figure 9. Brain regions showing significantly higher activation during preconscious exposure to neutral faces as compared to scrambled faces in DIDep compared to CONep (DIDep-CONep, N-S). The saggital view depicts areas in the dorsal brainstem, occipitotemporal junction, and parahippocampal gyrus. Activation in the visual cortex can be seen in the coronal view. Corresponding regions, cluster-sizes, MNI coordinates, and t-values can be found in Table 4.

Table 4. ANP/EP effects between groups in response to masked angry and neutral faces as compared to scrambled faces (A-S, N-S)

			MNI coordinates[a]				
Condition A-S	Brain area	Side	*x*	*y*	*z*	k*E*	*T* value
DIDanp - CONanp	n.s.						
CONanp - DIDanp	n.s						
DIDep - CONep	Precentral gyrus (primary motor cortex)	L	-36	-14	40	21	4.31
CONep - DIDep	n.s.						
Condition N-S							
DIDanp - CONanp	n.s.						
CONanp - DIDanp	n.s.						
DIDep - CONep	Brainstem (dorsal part)[c]	L	-12	-26	-18	1729	5.44*
	Parahippocampal gyrus (anterior part)	R	16	-10	-24	35	5.29
	Middle frontal gyrus	R	40	32	32	267	5.26*
	Middle frontal gyrus	L	-28	32	48	136	5.26*
	Middle temporal gyrus	R	62	-38	-8	81	4.86*
	Pre-SMA	L	-2	4	62	159	4.85*
	Precentral gyrus (primary motor cortex)	R	42	-10	44	386	4.83*
	pMCC/dPCC		0	-26	32	274	4.74*
	DMPFC	R	2	56	24	166	4.53*
	Middle temporal gyrus[b]	R	60	-22	-12	54	4.50
	Precentral gyrus (primary/premotor cortex)	L	-36	-14	42	46	4.34
	STS	L	-58	-16	-6	13	4.32
	Lateral occipital cortex (inferior part)	R	54	-68	0	24	4.21
	Occipital pole (peristriate cortex)	R	28	-96	-2	7	4.12
CONep - DIDep	n.s.						

Note. R/L, left or right hemisphere; k*E*, cluster-size in voxels (one voxel is 2x2x2mm); n.s., not significant; DIDanp, ANP DID group; DIDep, EP DID group; CONanp, ANP control group; CONep, EP control group; Pre-SMA, pre-supplementary motor area; pMCC, posterior midcingulate cortex; dPCC, dorsal posterior cingulate cortex; DMPFC, dorsomedial prefrontal cortex; STS, sulcus temporalis superior

[a] MNI coordinates (in mm) refer to the maximum of signal change in each region

[b] ventral bank of the sulcus temporalis superior

[c] cluster includes Brainstem R, Parahippocampal gyrus L, Lingual gyrus R/L, Temporal occipital fusiform gyrus L, Occipital fusiform gyrus L

* corrected for multiple comparisons using cluster-level statistics, $p < .05$

Table 5. Dissociative-part effects between groups in response to masked neutral faces as compared to scrambled faces (N-S)

			MNI coordinates[a]				
Condition N-S	Brain area	Side	*x*	*y*	*z*	k*E*	*T* value
DIDep - CONep	Brainstem	L	-12	-26	-18	42	5.44**
	Middle frontal gyrus	R	40	32	32	35	5.26**

Note. R/L, left or right hemisphere; k*E*, cluster-size in voxels (one voxel is 2x2x2mm); DIDep, EP DID group; CONep, EP control group

[a] MNI coordinates (in mm) refer to the maximum of signal change in each region

** FWE correction for whole-brain multiple comparisons, $p < .05$ (k$E = 7$)

5.1.5. Discussion

This is the first fMRI study of neural activation patterns to preconsciously perceived facial expressions for two different prototypes of dissociative parts of the personality (ANP and EP) in DID patients. As generally hypothesized, we found different neural and behavioral activation patterns for ANP and EP in DID patients and in controls.

Consistent with our first hypothesis, as EP, DID patients demonstrated more activation in the right parahippocampal gyrus during the masked presentation of neutral and angry faces than they had as ANP (see **Table 3**). The parahippocampal gyrus has been implicated in recall of autobiographical memories (Fink, et al., 1996), with a right hemispheric predominance (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994), and in re-experiencing symptoms in PTSD (Osuch, et al., 2001; Sakamoto, et al., 2005). The observed enhanced activation in the parahippocampal gyrus corresponds with core features of EP, that is, their fixation in traumatic memories, their tendency to perceive safe individuals as dangerous, and their tendency to reactivate traumatic memories when confronted with reminders of traumatic experiences. However, we did not find the hypothesized differences for ANP and EP in DID patients with respect to visual areas, face sensitive areas, amygdala, and motor areas. This negative finding may at least in part relate to limitations of the present study, which will be discussed below.

Differences in neural activation patterns were much more pronounced for EP in DID patients compared to EP in controls. But in contrast with our third hypothesis, EP's subliminal perception of neutral and not angry faces revealed these strong differences. In reaction to subliminally presented angry faces, EP in DID showed enhanced activity in the precentral gyrus (see **Figure 9**). We also observed increased activity in the temporal pole of the superior temporal gyrus. This area is known to participate in the analysis of faces too, particularly in processing the semantic knowledge of a face (Haxby, et al., 2000). We are reluctant to discuss this activity any further, as it did not reach the statistical threshold for non-a priori defined regions. Masked neutral faces evoked activation in a cluster of brain areas including the dorsal brainstem, parahippocampal gyrus, and mainly left lateralized areas positioned in the occipito-temporal junction (see **Figure 9**), as well as several motor-related areas (see **Table 4**).

Taken together, the findings of the current study suggest that as EP, DID patients deeply engaged in subliminally presented faces, particularly in neutral faces. DIDep's dorsal brainstem activity furthermore indicates increased arousal (Jones, 2003) and associated vigilance in reaction to subliminally perceived neutral faces.

The occipito-temporal junction is a face-sensitive region (Gorno-Tempini, et al., 2001; Haxby, et al., 2000; Nakamura, et al., 2000), and the occipital fusiform gyrus contributes at a very early phase in the face-processing stream and generates the initial representation of a face (Pitcher, Walsh, Yovel, & Duchaine, 2007). The mainly left lateralized activation pattern is in line with previous findings of left hemispheric involvement in subliminal perception of faces (Henke, Landis, & Markowitsch, 1994). Activation of motor areas could indicate defensive reactions to perceived threat.

Given the integral role of the amygdala in automatic processing of threatening stimuli (Öhman, 2005; Vuilleumier, 2005), the reason for the lack of amygdalar activity in our study deserves a closer look. PTSD neuroimaging studies have led to inconsistent findings with regards to amygdala activation. Studies employing masked-faces paradigm (Rauch, et al., 2000) or visual imagery (Shin, et al., 1997) demonstrated exaggerated amygdala responses in PTSD patients compared to healthy controls, although studies conducting script-driven imagery failed to reveal increased amygdala activity in PTSD subjects (Bremner, Narayan, et al., 1999; Bremner, Staib, et al., 1999; Shin, et al., 1999). Furthermore, amygdala engagement during the processing of fearful faces is a reliable and consistent finding in the fMRI literature, whereas amygdala enhancement as reaction to angry or neutral faces has been reported less consistently (Fusar-Poli, et al., 2009). The amygdala can habituate during repeated exposure to emotional stimuli (Breiter, et al., 1996; Fischer, et al., 2003; Schwartz, et al., 2003; Wright, et al., 2001). Time courses of left and right amygdala activity (mean beta values within the left and right amygdala, data not shown) did not reveal evidence of amygdala habituation during the whole experimental period, neither in DID patients nor in controls. However, the amygdala is not only restricted to signaling of fear, but is also involved in the evaluation of salient (Sander, Grafman, & Zalla, 2003) and novel stimuli (Blackford, Buckholtz, Avery, & Zald, 2010). It has been shown that the amygdala is activated most strongly at the beginning of a stimulus series (Büchel, Morris, Dolan, & Friston, 1998). Hence,

the blockwise manner, in which our stimuli were presented, might explain the non significant amygdala activity in our study. It could also be possible that the amygdala of DID patients was consistently overactivated even before negative stimuli were presented. This idea accords with results of other imaging studies showing that anxious individuals have increased anticipatory activity in the amygdala preceding stimuli with prior known negative, neutral, or ambiguous emotional valence (Brühl, et al., 2011; Nitschke, et al., 2009).

Comparisons in which ANP's brain activation was contrasted to other conditions did not give significant results (i.e., DIDanp-DIDep, DIDanp-CONanp; see **Table 3** and **4**). This finding indicates a relatively decreased BOLD signal all over the brain for this type of dissociative part, suggesting low involvement in subliminally presented faces.

There was increased activation in many a priori defined brain regions for EP in DID patients compared to EP in controls, but fewer differences for ANP in DID patients compared to EP in these patients. We therefore checked post hoc if these differences also existed for ANP in DID patients compared to EP in controls (DIDanp-CONep N-S, data not shown). We found enhanced activity in the dorsal brainstem, lingual gyrus (with some voxels extending to the temporal occipital fusiform gyrus), and motor-related areas such as the putamen and the (pre-)supplementary motor area. While this pattern resembles the one for DIDep, it was less pronounced. It thus seems that ANP's decreased involvement in consciously perceived trauma-related cues (Reinders, et al., 2003; Reinders, Nijenhuis, et al., 2006) has roots in ANP's subdued preconscious reactivity to trauma-related cues.

This study is the first to document that foremost as EP, DID patients specifically focus on, and seem to be alarmed by preconsciously perceived neutral faces. Consistent with the neural findings and our fourth hypothesis, EP in DID patients also showed significantly slower RTs to neutral faces and a tendency to slower RTs to angry faces compared to ANP in DID patients and EP in controls (see **Figure 7**). This face- and dissociative part-specific effect could also be observed in the direct comparison between RTs related to neutral and angry faces. This comparison yielded a significantly longer RT in the neutral face condition in EP of DID patients only (see **Figure 8**).

Emotionally neutral faces may be threatening to them for a variety of reasons. First, it can be hard to disambiguate these expressions ("what does this face mean?"), particularly following emotional neglect ("this person may not care about me") and abuse ("this person seems calm, but for how long, what emotion will he or she show next?"). Consistent with this interpretation, patients with borderline personality disorder (BPD) regarded neutral faces as threatening, and demonstrated a hyperactivated amygdala when supraliminally confronted with these faces (Donegan, et al., 2003). BPD, DID, and dissociative symptoms are all intimately related to a context of unstable and disrupted interpersonal relationships (Benjamin, 1993; Dutra, et al., 2009; Kelley, et al., 2002; Korol, 2008; Linehan, 1993; Ogawa, et al., 1997). As the type of dissociative part of the personality that is fixed in the traumatic past, EP may regard neutral faces as untrustworthy and threatening, and thus become hypervigilant when confronted with them, and prepare motor defensive reactions. Neutral faces can also express affective unavailability (of caretakers), a condition that all DID patients in the study reported (neglect and abuse by family members). The quality of the early caregiving relationship is linked to dissociation in that affective parental unavailability and disorganised attachment in childhood are major predictors of dissociative symptoms in adulthood (Dutra, et al., 2009; Ogawa, et al., 1997). Our results fit findings of grave effects of still faces on children (Mesman, Van IJzendoorn, & Bakermans-Kranenburg, 2009; Tronick, Als, Adamson, Wise, & Brazelton, 1978), particularly in individuals who are neglected, abused, and insecurely attached. They generally add to the evidence for a pivotal role of emotional neglect and emotional unavailability of caretakers in DID.

Our data contrast with the findings of Hermans et al. (2006), who reported longer RTs to angry compared to neutral faces in EP of DID patients. This conflicting finding might be related to several methodological differences between these studies in relation to stimulation, such as the facial and masking stimuli, the design of the subliminal presentation, and the presentation time. While our study presented facial stimuli for 16.7 msec, Hermans et al. presented these stimuli for 25 msec. Cognitive theories of anxiety maintain that the attentional bias toward threatening material occurs at a preconscious level (Cisler & Koster, 2010). The stage of sensory reactivity at which this bias emerges in DID has not been investigated systematically to date. There is neurophysiological evidence showing that the signals transmitted by

neurons in the visual cortex increase as a function of stimulus length (Rolls, Tovee, & Panzeri, 1999). In other words, the shorter the presentation time, the less sensory signals for the discrimination of a face are provided. Neutral faces have an uncertain emotional valence and, therefore, require deeper processing demands. It might be speculated that the slightly shorter presentation time in our study particularly increased preconscious fixation in EP on neutral facial expressions, as EP is focused on threat or potential threat cues (Van der Hart, et al., 2006). Future studies are needed to test this hypothesis.

Our fifth and last hypothesis was that the identified behavioral and neural differences for ANP and EP in DID patients would not be matched by controls, who were instructed and motivated to simulate ANP and EP. Controls showed a tendency to inverse RTs and neural activation patterns for these different prototypical parts. That is, as ANP, the actors tended to react like EP in DID patients, and as EP like ANP in these patients. The actors were thus unable to simulate DID with respect to behavioral and neural reactivity, which contradicts the sociocognitive model of DID. Compared to EP, as ANP, controls had amygdala activity in the neutral face condition (see **Table 3**), but neither brainstem activity nor a longer RT. Whereas the neutral faces were thus salient (Davis & Whalen, 2001; LeDoux, 1998) for ANP-simulating controls, they did not arouse them or attract much preconscious attention, as happened for authentic EP. The current findings add to the psychobiological evidence (Hermans, et al., 2006; Reinders, et al., 2012) that DID is neither an effect of suggestion and fantasy, nor of role-playing.

The findings have strong implications for the clinical context in dealing with DID patients and suggest that therapists of DID patients must be emotionally and behaviorally engaged. Therapeutic neutrality will probably scare them, particularly as EP, triggering and reinforcing conditioned emotional and defensive reactions. As EP, these patients will tend to perceive an emotionally neutral therapist as an emotionally unavailable caretaker. These effects may not be immediately visible when an ANP is dominant due to ANP's mental avoidance and under-engagement. However, ANP and EP can be activated in parallel (Van der Hart, et al., 2006), so that the therapist's neutrality can nonetheless affect the patient as one or more EPs. This interpretation is consistent with clinical observations (Van der Hart, et al., 2006). For example, ANP may report that EP is negatively affected by the therapist's neutrality. It may also

happen that ANP does not notice or report this emotionality in an EP, but that EP responds in the described emotional sense in a later stage, while expressing that she/he felt rejected, confused, or afraid when the therapist was emotionally un(der)engaged.

This study has several limitations. Our sample size was relatively small. This was due to the difficulty in finding DID patients who are able to alternate between ANP and EP at request and to remain activated, particularly as EP, for a substantial period of time in an fMRI environment. Patients who can perform this feat are the ones who have been in treatment for at least several years. Because treatment of DID fosters integration between the different dissociative parts and integration of traumatic memories, studies such as ours are prone to underestimate naturally existing biopsychosocial differences between these subsystems of the personality. In order to check if the actors had understood and followed the instructions to simulate an ANP and EP, patients and controls completed as ANP and EP the STAI-S (Laux, et al., 1981) immediately after the fMRI measurement. Explorative data analysis revealed that, in contrast to the behavioral and neural data, no inverse simulation pattern could be observed (see **Table 1**). That is, as ANP, the actors tended to react like ANP in DID patients, and as EP like EP in these patients. However, no significant differences were observed between and within groups. Therefore, the STAI-S does not seem to be an appropriate measurement to examine adherence to simulation instructions. In future studies, other assessments such as self-report should be included. DID patients have considerable comorbidity (Ellason, Ross, & Fuchs, 1996). Future studies will need to evaluate axis I and axis II comorbidity and address covariations between this comorbidity and patterns of neural activation. Another limitation of the study is that only two of our patients were free of medication. Medication washout is not feasible with DID patients. However, medication does not explain the observed differences between ANP and EP in DID patients.

In conclusion, the current study shows that two prototypical parts of the personality in DID patients, ANP and EP, have different biopsychosocial reaction patterns to backward masked neutral and angry faces that controls were unable to simulate. Fixed in active defense, as EP, DID patients engage in early and automatic scanning of facial expressions. Avoiding threat cues, as ANP, they are underinvolved

in the faces. These results and interpretations are consistent with clinical observations and TSDP, but inconsistent with the sociocognitive model of DID.

5.1.6. Supplementary Findings

Supplementary Findings 1

Determination of awareness: subjective measurement

Participants were as ANP and EP invited to report what they saw on the screen during the fMRI measurement. Apart from one EP, who reported seeing evil grimaces, all dissociative parts of the personality only described the black-and-white dotted mask and the colored dots. Because two EPs in a previous study (Hermans, et al., 2006) also detected backward masked faces, it may be that some EPs are extraordinary hypervigilant regarding potential threat cues, and therefore detect even impressions of faces that for other individuals and for ANP remained below the level of conscious awareness. Still, this EP's hit rate for the objective measurement described below (42.85%) was comparable to the mean hit rate of the patient group (see **Supplementary Table 1**).

Determination of awareness: objective measurement

Following the fMRI measurement, patients (functioning as ANP) and controls were subliminally presented 56 faces (14 stimuli per face condition) on the screen inside the scanner room, using the same lighting conditions. After the subliminal presentation of each face, we supraliminally projected this target face together with a randomly chosen face matched in sex and emotional expression, and requested the participants to say or guess which of these two faces had been previously projected subliminally. Due to technical problems, one Presentation logfile of an actor was not stored and could not be used for the statistical analysis. The mean hit rate for patients as well as controls was approximately 50% (see **Supplementary Table 1**), implying a level of detectability at chance level (Kihlstrom, et al., 1992). Hence, the participants had not consciously seen the experimental faces.

Supplementary Findings 2

We examined the projector's capacity, using a light sensor (Vishay Semiconductors), to project pictures within the refresh rate of the computer's graphic card (NVIDIA Quadro FX 1700, 60-Hz). The sensor was fixed on the screen while the computer was running a sequence of alternating black-and-white images with a presentation time of 16.67 msec. The sensor's output was measured by a digital oscilloscope (APS 230). The actual presentation time of the projector was around 16.5 msec ± 2 msec. It thus projected the subliminal pictures within the critical time limit.

Supplementary Table 1. Objective determination of awareness (forced-choice task) in ANP

	DID patients (n=15)	Controls (n=14)
Hits (%)	50.71±9.66	51.28±9.67

Note. DID, Dissociative identity disorder; mean percentage hit ± 1 SD is reported

5.2. Experiment 2: Resting-state paradigm

Dissociative part-dependent resting-state activity: A controlled fMRI perfusion study of dissociative identity disorder

Submission to a peer-reviewed journal intended

Authors:

Yolanda R. Schlumpf, MSc[a], A. A. T. Simone Reinders, PhD[b,c], Ellert R. S. Nijenhuis, PhD[d], Roger Luechinger, PhD[e], Matthias J. P. Van Osch, PhD[f], Lutz Jäncke, PhD[a,g]

a Division of Neuropsychology, Institute of Psychology, University of Zurich, Switzerland

b Department of Neuroscience, University Medical Center Groningen, and BCN Neuroimaging Center, University of Groningen, Groningen, The Netherlands

c Department of Psychosis Studies, Institute of Psychiatry, King's College London, London, United Kingdom

d Top Referent Trauma Center Mental Health Care Drenthe, Assen, The Netherlands

e Institute for Biomedical Engineering, University and ETH Zurich, Switzerland

f Department of Radiology, C.J. Gorter Center for High-Field MRI, Leiden University Medical Center, Leiden, The Netherlands

g International Normal Aging and Plasticity Imaging Center, University of Zurich, Switzerland

Keywords: dissociative identity disorder, arterial spin labeled perfusion, resting-state, default mode activity, self-referential processing

Acknowledgments: This research was supported by the Forschungskredit of the University of Zurich. A.A.T.Simone Reinders is supported by the Netherlands Organization for Scientific Research (www.nwo.nl), NWO-VENI grant no. 451-07-009. We would like to thank the colleagues of Prof. Jäncke's lab for their helpful comments and Franz Liem for his technical support. We are indebted to Ekaterina Weder and Eva Zimmermann for their collaboration as research clinicians. Special thanks go to the patients and their therapists for participating in the study.

5.2.1. Abstract

Background: In accordance with the Theory of Structural Dissociation of the Personality (TSDP), studies of dissociative identity disorder (DID) have documented that two prototypical dissociative subsystems of the personality, known as the "Emotional Part" (EP) and the "Apparently Normal" Part (ANP), have different psychobiological reactions to supraliminal and subliminal trauma-related cues. High and low fantasy prone controls instructed and motivated to simulate ANP and EP in DID had different neural and psychophysiological reactions.

Methods: Arterial spin labeling perfusion magnetic resonance imaging was used to test the hypotheses that ANP and EP in DID have different perfusion patterns in response to instructions to relax and lay immobile in a brain scanner, and that perfusion is different in ANP and EP simulating actors.

Results: Perfusion ($p<0.001$, uncorrected for multiple comparisons) was dependent on ANP and EP in DID patients. Compared to EP, ANP showed increased thalamus activity, and compared to ANP, EP had increased perfusion in the dorsomedial prefrontal cortex, primary somatosensory cortex, and several motor-related areas. Perfusion patterns for the simulated ANP and EP were different. Fitting their reported role-play strategies, the actors activated brain structures involved in visual mental imagery and empathizing feelings.

Conclusion: DID involves ANP and EP dependent neural resting-state differences. Compared to ANP, EP activated brain structures involved in self-referencing and sensorimotor actions more. Controls motivated and instructed to simulate ANP and EP had different perfusion patterns. The findings are consistent with TSDP and inconsistent with the idea that DID is caused by suggestion, fantasy proneness, and role-playing.

5.2.2. Introduction

Consistent clinical observations and retrospective findings indicate that dissociative identity disorder (DID) (American Psychiatric Association, 1994) is intimately related to severe traumatization including emotional neglect (Van der Hart, et al., 2006). This conclusion is supported by the results of prospective longitudinal research of dissociation (Diseth, 2006; Dutra, et al., 2009; Ogawa, et al., 1997). Whereas most theories of DID include traumatization as one of the causal factors of the disorder, the sociocognitive model of DID entails the idea that the disorder is caused by suggestion, fantasy proneness, and role-playing (Lilienfeld, et al., 1999; Merskey, 1992; Piper & Merskey, 2004; Spanos, 1994). However, studies showing that DID can be caused by these factors is lacking, and patients with DID are not particularly fantasy prone (Reinders, et al., 2012). In addition, mentally healthy women (Hermans, et al., 2006), high and low fantasy prone women (Reinders, et al., 2012), and actors (Schlumpf, et al., 2013) who were motivated and instructed to simulate two different prototypes of dissociative parts were unable to simulate the psychophysiological and neural activation patterns of these dissociative parts in women with DID.

Several studies have compared psychobiological reactions of different dissociative parts in DID, but advances in the field critically depend on theoretical predictions with respect to the kind of biopsychosocial differences that exist among different types of dissociative subsystems or “parts“ of the personality as a whole biopsychosocial system (Nijenhuis, et al., 2002). The Theory of Structural Dissociation of the Personality (TSDP) offers such hypotheses (Nijenhuis & Den Boer, 2009; Nijenhuis, et al., 2002; Van der Hart, et al., 2006). The two major prototypes that TSDP distinguishes are metaphorically referred to as “Emotional Parts” (EP) and “Apparently Normal Parts” (ANP) of the personality. As ANP, DID patients aim to fulfill functions in daily life, and in this context they try to mentally and behaviorally avoid traumatic memories and other trauma-related stimuli. ANP, thus, has not or not sufficiently personified traumatic experiences and memories, can have a degree of amnesia regarding the traumatic past, and is to some degree depersonalized and bodily numbed. As EP, DID patients are fixated on traumatic memories, that is, in nonintegrated sensorimotor and emotional reenactments of traumatizing events. There are two major subtypes of EP (Nijenhuis & Den Boer,

2009). One subtype tends to engage in active mammalian defenses (e.g., freeze, flight, attachment cry) and strong emotions, such as intense fear, in reaction to actual or perceived threat. These reactions involve dominance of the sympathetic nervous system. As this subtype, DID patients are generally self-conscious, emotional (e.g., fearful), body-oriented, and hyperaroused. The other subtype of EP predominantly engages in passive mammalian defense (playing dead, tonic immobility) to actual or perceived threat. This kind of defense would imply a degree of parasympathetically mediated hypoarousal, emotional numbing, and bodily anesthesia.

TSDP is based on clinical and empirical evidence (Nijenhuis & Den Boer, 2009; Van der Hart, et al., 2006). For example, in a Positron Emission Tomography (PET) study, DID patients listened as ANP and as EP to audiotaped descriptions of a neutral autobiographical memory that these dissociative parts shared, as well as to a description of a traumatic memory that was only autobiographical for EP (Reinders, et al., 2003; Reinders, Nijenhuis, et al., 2006). ANP and EP (in Reinders, Nijenhuis, et al. (2006) referred to as neutral identity state and trauma-related identity state, respectively) had different psychophysiological and neural reaction patterns to the trauma script. In line with TSDP, as ANP, the patients had a brain activation pattern similar to patients with depersonalization disorder (Simeon, et al., 2000) and PTSD patients with negative dissociative symptoms to trauma-related stimuli (Lanius, et al., 2006; Lanius, et al., 2002). ANP had highly similar reaction patterns to the neutral and the trauma script, which indicates a low emotional involvement in the trauma script. As EP (subtype active defense), patients were deeply emotionally and bodily engaged in this script. In contrast with ANP, EP had activation in many brain areas also observed in PTSD patients who were confronted with a personalized trauma script and who reacted with positive symptoms such as hyperarousal (Lanius, et al., 2001; Rauch, et al., 1996; Shin, et al., 2001). As EP but not as ANP, DID patients showed a significant increase in heart rate and blood pressure and a significant decrease in heart rate variability in reaction to the trauma script. In sum, EP was psychobiologically hyperaroused, and ANP was underengaged.

The same paradigm was repeated with healthy matched controls (Reinders, et al., 2012). Neither high nor low fantasy prone, mentally healthy women instructed and motivated to simulate ANP and EP had the psychophysiological and neural activation patterns of the genuine ANP and EP in DID patients. This finding contradicts the

sociocognitive view of DID (Giesbrecht, et al., 2008; Lilienfeld, et al., 1999; Merckelbach, Devilly, et al., 2002; Merckelbach & Muris, 2001; Merskey, 1992; Spanos, 1994).

Using a conjunction analysis (Price & Friston, 1997; Price, Moore, & Friston, 1997), Reinders, Nijenhuis et al. (2006) demonstrated that ANP and EP were associated with two different neural networks that are independent of the type of the memory script they listened to. The authors suggested that these networks might be involved in functioning as two different prototypes of dissociative parts. If this idea holds, ANP and EP should have different neural characteristics when instructed to rest, that is, to relax, close their eyes, and lay immobile on the back in the narrow enclosed MRI space with their head fixed, and without the distraction of a more specific task. According to TSDP, this assignment is emotionally challenging for DID patients, as most of them have been chronically abused and emotionally neglected. The situation would be particularly demanding for them as EP. The experimental procedure could trigger trauma-related memories, in which EP is fixated, and that ANP attempts to avoid.

The study of resting-state neural activity has recently become an important area of neuroimaging. Of special interest is the so called default mode network (DMN), a set of brain areas consisting of the medial prefrontal cortex (MPFC), posterior cingulate (PCC) in addition to midline parietal structures, lateral parietal regions, and medial and lateral temporal lobes (Gusnard & Raichle, 2001; Raichle, et al., 2001; Raichle & Snyder, 2007). The DMN is activated in response to rest instructions and is deactived during the execution of goal-directed tasks (Fox, et al., 2005; Fransson, 2005; Greicius, Krasnow, Reiss, & Menon, 2003; Greicius & Menon, 2004; Mazoyer, et al., 2001; Shulman, et al., 1997; Tian, et al., 2007). Converging evidence suggests that the DMN is critical for general self-referential processing, such as autobiographical memory, self-reflection, self-awareness (i.e. introspection), and stimulus-independent thought (Andrews-Hanna, et al., 2010; Buckner, et al., 2008; Mason, et al., 2007; Northoff, et al., 2006).

The goals of the current study were to examine and compare brain perfusion patterns for ANP and EP in DID patients and ANP and EP in simulating actors following the rest instructions described above. Rest instructions do not imply that the participants are actually resting. The term resting-state thus merely refers to the state

that rest instructions elicit. The comparison of patients and controls was to test the idea that DID involves suggestion and role-playing rather than a trauma-related condition (Merckelbach, Devilly, et al., 2002; Merskey, 1992).

To date, no study investigated so called resting-state perfusion differences in ANP and EP in DID. A Single-Photon Emission Computed Tomography (SPECT) study yielded bilateral orbitofrontal hypoperfusion and left lateral hyperperfusion during rest for a type of dissociative part in DID described as the "host" compared to healthy volunteers (Sar, et al., 2001). No significant perfusion differences were observed between the host, defined as the dissociative part of the personality that is most of the time present during a usual day (Putnam, 1997), and a different type of dissociative part. We suspect that in most cases, the host was an ANP, but it is unclear if the "alter" involved a second ANP, or an EP. Sar et al. (2001) may have compared two ANP's rather than an ANP and an EP. If so, this may explain why they did not find different patterns of brain activity for the tested dissociative parts.

A different but not incompatible possibility is that SPECT is insufficiently sensitive to measure perfusion differences in response to rest instructions. In the current study, we used more sensitive arterial spin labeling (ASL), which generates PET-like images without the need of a radioactive tracer. ASL provides a quantitative CBF measurement, and is therefore particularly useful in the investigation of individual differences in brain metabolism (Detre, et al., 2012).

Considerations based on TSDP and previous research findings lead us to hypothesize that (i) there are perfusion differences for DID patients and simulating controls. In particular, we predicted that (ia) compared to the controls, DID patients show relative higher activation in areas which commonly exhibit increased neural activity following rest instructions (default mode activity). Looking at the comparison from the other side, we hypothesized that (ib) controls compared to DID patients elicit a brain pattern distinct from the default mode activity because according to TSDP, simulating an ANP and EP and being a genuine ANP and EP constitute different mental states. We furthermore hypothesized that in response to the described rest instructions, (ii) ANP and EP in DID have different patterns of brain perfusion and that (iii) comparisons of ANP and EP simulating controls yield different neural reactivity patterns than comparisons of ANP and EP in DID patients.

5.2.3. Methods

Participants

Fifteen female DID patients were included in the study. This sample was also used in a study on the functional correlates of subliminally presented faces (Schlumpf, et al., 2013). We enrolled Swiss and German patients, who were recruited from private practitioners of psychiatry and psychotherapy and psychiatric outpatient departments. All participants fulfilled the diagnostic criteria of DID according to DSM-IV (American Psychiatric Association, 1994). For the sake of the study, the clinical diagnoses were independently checked by experts in dissociative disorders using the German version of the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D) (Steinberg, 1993), the (SKID-D) (Gast, et al., 2000). The therapy of the participating patients had to have progressed to a treatment phase involving exposure to trauma-related memories (Steele, et al., 2005; Van der Hart, et al., 2006). Individuals with any of the following conditions were excluded: comorbid psychosis, drug abuse or addiction, antisocial or histrionic personality disorder, and a neurological or organic brain disease. Thirteen patients were medicated at the time of the measurement, predominantly with antidepressant medication. Two patients were free of medication.

The control group consisted of fifteen female actors, who were motivated to simulate ANP and EP. There were no significant differences between the control and patient group in age (controls: M=43.2 years, SD=10.4; patients: M=43.3 years, SD=9.1; $t(28)=0.019$, $p>0.05$) and educational level (controls: M=4.7, SD=1.2; patients: M=4.1, SD=1.5; $t(26.099)=-1.341$, $p>0.05$; the educational level was assessed by a 7-point Likert scale based on the common European educational system). To ensure that none of the controls had a dissociative disorder, PTSD, and/or major depression, the controls completed the German version of the Posttraumatic Diagnostic Scale (PDS) (Ehlers, et al., 1996) and the Beck Depression Inventory II (BDI-II) (Hautzinger, et al., 2006) and were interviewed by clinical experts in dissociative disorders using the SKID-D (Gast, et al., 2000). The actors were carefully informed about the characteristics of ANP and EP using written information on TSDP (Van der Hart, et al., 2006). They also watched a video showing a DID patient, who alternates between ANP and EP. The controls were instructed and

motivated to create an ANP and EP and were requested to practice simulating ANP and EP as often as they deemed necessary to effectively simulate ANP and EP, but at least three times before the MRI measurement. Each subject was informed about risks and inconveniences associated with the experiment. All subjects gave written informed consent. The local ethics committee (cantonal ethical commission of Zurich) approved the study in compliance with the Helsinki Declaration.

Experimental design and procedure

The subjects were instructed to relax with their eyes closed and to stay motionless during the functional magnetic resonance (fMRI) measurement. All participants were first tested as ANP and next as EP, because starting with the less anxious dissociative part might be less demanding for them. The switch between the different dissociative parts of the personality took place outside the scanner, if needed with minimal guidance from the research clinician. To check for inadvertent switches to a different dissociative part than the intended ANP or EP, we asked the participants after each run what part had been present during the measurement. One ANP and two EP runs had to be repeated due to a switch to and/or a co-activation of an unintended dissociative part.

Image acquisition and data preprocessing

All magnetic resonance imaging (MRI) data were obtained at the University Hospital of Zurich with a 3-T Philips Achieva whole-body magnetic resonance imaging equipped with an eight-channel Philips SENSE head coil. Resting regional cerebral perfusion (rCBF) images were acquired with a pseudo-continuous ASL (p-CASL) sequence with background suppression (saturation of the imaging slice preceding the labeling and inversion pulses 1680 msec and 2760 msec after the saturation pulse) and a single shot echo-planar imaging (EPI) readout (TR/TE=4180/12 msec, SENSE factor 2.5). The duration of the labeling was 1650 msec and the image was acquired after a delay of 1525 msec. The sequence consisted of 23 slices of 6mm slice thickness acquired in ascending order with a 3x3mm^2 in-plane resolution. During a single run, 35 pairs of control/label image volumes were measured over a total scan

time of 5 minutes. An additional M0 image was acquired for measurement of the magnetization of arterial blood (same sequence as ASL without labeling or background suppression, TR=10s). A 3D MPRAGE T1-weighted anatomical scan was acquired for anatomical reference and post-processing.

The data of three controls and one patient were excluded due to huge movement artifacts and low signal quality. One patient reported to have fallen asleep during the ANP and to have switched several times during the EP run. One patient was not able to undergo the MRI measurement, and the data of one patient were lost due to a storage failure at the MRI center. The final brain imaging statistical analysis was performed with data of 11 participants in the patient group and 12 in the control group.

Resting-state rCBF maps were calculated using in-house programmed MATLAB scripts performing a simple pair-wise subtraction of control and label images (Van Osch, et al., 2009). Further analyses were performed with the statistical parametric mapping software SPM8 (http://www.fil.ion.ucl.ac.uk/spm). rCBF maps were normalized to the EPI template (Wastling, et al., 2009), which transformed them into MNI space (new voxel size=2x2x2mm^3). The normalized rCBF maps were spatially smoothed with an 8-mm full width at half-maximum (FWHM) Gaussian kernel.

The preprocessed data were analyzed using a flexible factorial design that consisted of two independent variables resulting in a 2×2 ANOVA with repeated measures on the second factor: Group (two levels: DID/CON), Type of dissociative part of the personality (two levels: ANP/EP). The second factor will be referred to as *Type* in the rest of the article. In order to correct for biological variation in total CBF, the mean gray matter (GM) CBF was included in the analysis as a covariate of no interest. The mean GM signal per subject was calculated over a GM mask obtained from the segmentation of the 3D T1 image by thresholding the GM probability images at 0.5. Only the GM signal was taken into account, as a previous study revealed that GM perfusion showed most variability between sessions (Gevers, et al., 2011).

The study design allows the calculation of various effects, i.e. main effect of Group, main effect of Type, and an interaction effect of Group by Type. Our main hypotheses were tested using one-sided t-tests. Group differences between the patients (DID) and controls (CON) were assessed with two two-sample t-tests (DID-

CON, CON-DID) based on the mean perfusion map of ANP and EP of every single participant. The participants were measured as ANP and EP in the patient group (DIDanp/DIDep) and in the control group (CONanp/CONep). Four planned comparisons consisting of Type effects between groups (DIDanp-CONanp, CONanp-DIDanp; DIDep-CONep, CONep-DIDep) and four planned comparisons consisting of Type effects within groups (DIDanp-DIDep, DIDep-DIDanp; CONanp-CONep, CONep-CONanp) were performed. An explicit binary mask provided by FSL (http://www.fmrib.ox.ac.uk/fsl) was applied at the level of the statistical interference to remove extracranial voxels. The mask was normalized to MNI space and had the same dimension and voxel size as the rCBF maps.

We accepted uncorrected significant levels (i.e., voxel level of significance uncorrected [unc.] for multiple testing) of $p<0.001$ and a minimum cluster-size of 12 voxels due to the fact that the ASL signal has an inherently low signal to noise ratio (SNR) (Detre, et al., 2012). Statistical thresholds of similar sizes were used in previous resting-state perfusion (Schuff, et al., 2011) and BOLD (Yin, et al., 2011) fMRI studies. Only the most significant finding of a brain area and first peak of a cluster are reported in **Table 6** to **9**. The cluster locations were labeled using the Harvard-Oxford cortical and subcortical structural atlases (Desikan, et al., 2006) and by visual inspection on a high-resolution T1-weighted image in FSL. Subregions in the cingulate cortex were named according to Vogt's division based on cytoarchitectonic characteristics (Vogt, 2005). The results are restricted to activations in the GM, as white matter perfusion measurements are still challenging with ASL (Van Osch, et al., 2009).

5.2.4. Results

Repeated measures ANOVA

Results for the main effects and interaction effect are listed in **Table 6**. Significant rCBF differences for the Type main effect, independent of Group, and for the Group main effect, independent of Type, were found. In addition, significant perfusion differences were observed due to an interaction effect between Type and Group.

Table 6. Main effect of Group, main effect of Type (ANP/EP), and interaction effect on resting-state regional cerebral blood flow (rCBF)

			MNI coordinates[a]				
	Brain area	Side	*X*	*y*	*z*	k*E*	*F* value
Main effect of Group	Middle temporal gyrus (temporal pole)	L	-54	2	-24	74	26.81
	Precuneus	L	-10	-54	56	57	23.17
	Angular gyrus	R	48	-48	28	54	21.81
	Middle frontal gyrus	R	36	14	32	13	19.53
Main effect of Type	Pre-SMA	R	10	10	66	42	17.61
	Postcentral gyrus (primary somatosensory cortex)	R	56	-12	36	24	16.95
	DMPFC	R	14	64	32	35	15.63
	Superior parietal lobe	R	38	-56	62	13	15.50
Interaction effect	Lateral occipital cortex	R	52	-64	-12	14	17.69
	Thalamus	R	8	-16	4	44	17.48
	Postcentral gyrus (primary somatosensory cortex)	R	60	-16	36	32	16.67
	Putamen	R	24	6	12	24	16.17
	Central operculum	R	46	-2	10	14	14.40

Note. R/L, left or right hemisphere; kE, cluster-size in voxels (one voxel is 2x2x2mm); Pre-SMA, pre-supplementary motor area; DMPFC, dorsomedial prefrontal cortex
[a] MNI coordinates (in mm) refer to the maximum of signal change in each region

Group differences

Group differences are given in **Table 7**. In line with our first hypothesis, we found positive perfusion differences in the patient group compared to the control group (DID-CON) and positive perfusion differences in the control group compared to the patient group (CON-DID).

DID showed higher perfusion than CON in the temporal pole of the middle temporal gyrus, in medial posterior and lateral inferior parietal regions (precuneus, angular gyrus), and in the dorsomedial prefrontal cortex (DMPFC). In CON compared

to DID, we observed increased perfusion in the middle frontal gyrus and occipital fusiform gyrus.

Table 7. Group differences in resting-state regional cerebral blood flow (rCBF)

			MNI coordinates[a]				
	Brain area	Side	*x*	*y*	*z*	k*E*	*T* value
DID-CON	Middle temporal gyrus (temporal pole)	L	-54	2	-24	102	5.18
	Precuneus	L	-10	-54	56	87	4.81
	Angular gyrus	R	48	-48	28	99	4.67
	DMPFC	R	16	40	42	17	4.19
	Superior frontal gyrus	L	-20	14	46	25	4.02
CON-DID	Middle frontal gyrus	R	36	14	32	24	4.42
	Occipital fusiform gyrus	L	-36	-74	-16	25	4.10

Note. R/L, left or right hemisphere; kE, cluster-size in voxels (one voxel is 2x2x2mm); DID, patient group; CON, control group; DMPFC, dorsomedial prefrontal cortex
[a] MNI coordinates (in mm) refer to the maximum of signal change in each region

Planned comparisons

Between-group comparisons of Type (i.e., two different types of dissociative parts of the personality, ANP/EP) are listed in **Table 8**. Type comparisons within groups are given in **Table 9**. We found significant rCBF differences in all eight planned comparisons.

Between-group Type comparisons

Significant rCBF changes for both ANP and EP between the groups are in accordance with our first hypothesis.

Compared to CONanp, DIDanp was associated with more activation in the temporal pole of the middle temporal gyrus, in the lateral inferior and posterior medial parietal lobe (angular gyrus, precuneus), and dorsal posterior cingulate cortex (dPCC) (DIDanp-CONanp). In the inverse contrast (CONanp-DIDanp), we revealed a higher perfusion in the middle frontal gyrus. An increased activation in the temporal pole of the middle temporal gyrus, in the precuneus, and angular gyrus, found in the contrast DIDanp-CONanp, could also be observed in DIDep compared to CONep (DIDep-CONep). CONep compared to DIDep (CONep-DIDep) showed higher

activation in the right thalamus, middle frontal gyrus, hippocampus, occipital fusiform gyrus, and lateral occipital cortex.

Within-group Type comparisons

The second hypothesis that DIDanp and DIDep differ in resting-state perfusion could not been rejected, because we found significant rCBF differences in DIDanp-DIDep and DIDep-DIDanp. In line with our third hypothesis, comparisons of CONanp and CONep yielded different neural reactivity patterns than comparisons of DIDanp and DIDep.

DIDanp had more perfusion in the bilateral thalamus than DIDep (DIDanp-DIDep). In the inverse contrast (DIDep-DIDanp), we found increased perfusion in the primary somatosensory cortex and in several motor-related brain areas including the primary motor cortex and higher-order motor areas (pre-supplementary motor area [pre-SMA], premotor cortex). In addition, DMPFC hyperperfusion could be observed (**Figure 10**).

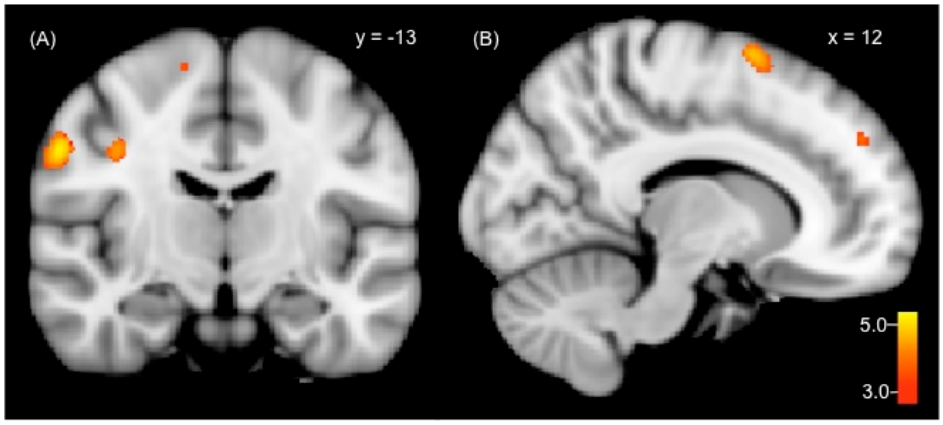


Figure 10. Significant rCBF increases in genuine EP (DIDep) compared to genuine ANP (DIDanp) in (A) the primary somatosensory cortex, primary motor cortex, premotor cortex and in (B) the pre-supplementary motor area (pre-SMA) and dorsomedial prefrontal cortex (DMPFC).

In CONanp compared to CONep (CONanp-CONep), we revealed higher brain activation in the bilateral thalamus and in extrastriate regions of the occipital pole. In the inverse contrast (CONep-CONanp), we observed a higher perfusion in insular-opercular regions (anterior insula, frontal operculum) and in inferior frontal areas (pars triangularis of the inferior frontal gyrus, orbitofrontal cortex [OFC]).

Table 8. Type (ANP/EP) effects between groups on resting-state regional cerebral blood flow (rCBF)

			MNI coordinates[a]				
	Brain area	Side	*x*	*y*	*z*	k*E*	*T* value
DIDanp - CONanp	Angular gyrus	R	46	-48	28	240	5.26
	Middle temporal gyrus (temporal pole)	L	-56	4	-26	87	4.80
	dPCC/Precuneus	R	8	-54	32	12	3.75
	Precuneus	L	-12	-52	58	25	3.63
CONanp - DIDanp	Middle frontal gyrus	R	34	14	30	39	4.02
DIDep - CONep	Precuneus	L	-14	-52	56	116	4.47
	DMPFC	R	6	40	40	51	4.43
	Angular gyrus	R	46	-48	28	37	4.05
	Superior frontal gyrus	L	-20	16	46	34	3.81
	Middle temporal gyrus (temporal pole)	L	-58	4	-26	23	3.63
CONep - DIDep	Thalamus	R	18	-22	16	60	3.94
	Middle frontal gyrus	R	36	14	32	16	3.93
	Hippocampus	R	32	-14	-26	27	3.67
	Occipital fusiform gyrus	L	-38	-74	-14	20	3.66
	Lateral occipital cortex	L	-38	-76	10	14	3.53

Note. R/L, left or right hemisphere; k*E*, cluster-size in voxels (one voxel is 2x2x2mm); DIDanp, ANP DID group; DIDep, EP DID group; CONanp, ANP control group; CONep, EP control group; dPCC, dorsal posterior cingulate cortex; DMPFC, dorsomedial prefrontal cortex

[a] MNI coordinates (in mm) refer to the maximum of signal change in each region

Table 9. Type (ANP/EP) effects within groups on resting-state regional cerebral blood flow (rCBF)

			MNI coordinates[a]				
	Brain area	Side	*x*	*y*	*z*	k*E*	*T* value
DIDanp - DIDep	Thalamus	R	10	-22	16	42	3.95
	Thalamus	L	-6	-22	16	13	3.52
DIDep - DIDanp	Postcentral gyrus (primary somatosensory cortex)	R	58	-14	36	139	5.18
	Pre-SMA	R	12	8	66	141	4.48
	Precentral gyrus (primary motor cortex)	R	38	-14	36	74	4.16
	DMPFC	R	14	48	34	41	4.06
	Superior parietal lobe	R	36	-56	64	26	3.71
	Precentral gyrus (premotor cortex)	R	16	-12	66	15	3.61
CONanp - CONep	Thalamus	R	8	-16	8	82	4.59
	Occipital pole (extrastriate cortex)	L	-10	-96	16	29	4.10
	Thalamus	L	-4	-2	2	40	3.90
	Occipital pole (extrastriate cortex)	R	24	-94	14	23	3.57
CONep – CONanp	Insula (anterior)	R	30	12	-16	102	4.87
	Frontal operculum	R	38	14	8	127	4.01
	Pre-SMA	L	-8	12	52	25	3.92
	Inferior frontal gyrus (pars triangularis)	L	-46	30	0	27	3.78
	Putamen	R	26	4	12	63	3.76
	Middle temporal gyrus (temporal pole)	L	-48	16	-34	19	3.66
	Central operculum	L	-34	6	14	38	3.65
	OFC	L	-26	8	-16	14	3.55
	Pallidum	L	-20	-6	-6	12	3.43

Note. R/L, left or right hemisphere; kE, cluster-size in voxels (one voxel is 2x2x2mm); DIDanp, ANP DID group; DIDep, EP DID group; CONanp, ANP control group; CONep, EP control group; Pre-SMA, pre-supplementary motor area; DMPFC, dorsomedial prefrontal cortex; OFC, orbitofrontal cortex
[a] MNI coordinates (in mm) refer to the maximum of signal change in each region

5.2.5. Discussion

This is the first fMRI perfusion study measuring brain perfusion in rest instructions in DID patients. As hypothesized, we found differences between DID patients and DID simulating actors, as well as between two different prototypes of dissociative parts of the personality (ANP and EP) in DID patients.

Compared to controls, DID patients showed higher resting-state metabolism in several areas belonging to the DMN (i.e, temporal pole of middle temporal gyrus, precuneus, angular gyrus, and DMPFC) (Raichle & Snyder, 2007). The default mode activity of DID is in line with our first hypothesis and suggests that DID patients were more involved in attending to their self-states when instructed to rest than controls.

In the inverse contrast (CON-DID), we found more perfusion in the middle frontal gyrus and in the occipital fusiform gyrus for the controls. Neural processes associated with intended and motivated role-playing of ANP and EP were clearly distinct from those correlated with being ANP and EP following rest instructions. The DMN is also called the “task-negative” network (Fox, et al., 2005). Whereas it shows attenuated levels of neural activity at rest and during self-referential processes (Andrews-Hanna, et al., 2010; Buckner, et al., 2008; Gusnard & Raichle, 2001; Mason, et al., 2007; Northoff, et al., 2006; Raichle, et al., 2001), this network exhibits activity decreases across many goal-directed tasks (Fox, et al., 2005; Fransson, 2005; Greicius, et al., 2003; Greicius & Menon, 2004; Mazoyer, et al., 2001; Shulman, et al., 1997; Tian, et al., 2007). Enacting ANP and EP involves a goal-directed task, which can explain the relative lower default mode activity for controls compared to DID patients.

The between-group Type effects fit these interpretations. Of special interest is the increased activity in the precuneus, angular gyrus, and temporal pole of the middle temporal gyrus for ANP and EP in DID patients when contrasted with the corresponding simulated ANP and EP (i.e., DIDanp-CONanp, DIDep-CONep). These areas are part of the DMN (Gusnard & Raichle, 2001). The precuneus is the area of the brain with the highest resting-state perfusion and with perfusion decreases during non-self-referential, goal-directed actions (Cavanna & Trimble, 2006). We therefore conclude that in contrast to the DID-simulating controls, the DID patients engaged as ANP and EP in self-referential actions following our relaxation instructions.

In line with our second hypothesis, we found different patterns of resting-state perfusion for ANP and EP in the patients. Consistent with TSDP, they specifically reported that not having a more explicit task to focus on while laying in the scanner was threatening. Compared to EP, ANP showed more metabolism in the bilateral thalamus (DIDanp-DIDep), and right thalamus activity was higher in controls simulating EP than in authentic EP (CONep-DIDep). However, controls simulating ANP also had more bilateral thalamus metabolism than controls simulating EP (CONanp-CONep). Whereas relatively high thalamus activity for ANP in DID patients may not be a DID-specific finding, our result parallels prior PTSD studies conducted under rest (Kim, et al., 2007) or using script-driven symptom provocation paradigms (Lanius, et al., 2005; Lanius, et al., 2001; Lanius, et al., 2003). Lanius et al. (2001, 2003, 2005) have reported that flashback/reliving PTSD patients (i.e., subjects characterized with positive dissociative/EP-like symptoms) had relatively decreased thalamic activation during the recall of traumatic memories, while “dissociated” PTSD subjects (i.e., subjects characterized with negative dissociative/ ANP-like symptoms) were associated with a relative increased thalamic activity. In the neurobiological model of Krystal and colleagues, the thalamus plays a central role (Krystal, Bennett, Bremner, Southwitck, & Charney, 1995). The idea is that sensory and arousal signals parallel in the thalamus, the brain structure that relays the transmission of bodily sensations to target brain areas, such as the prefrontal cortex and cingulate gyrus, being involved in affect regulation, and amygdala and hippocampus. Under condition of high arousal, this transmission is altered. Kim et al. (2007) found a positive correlation between right thalamic blood flow following rest instructions and the severity of current re-experiencing symptoms in PTSD patients (the more rCBF in the right thalamus decreased, the less reliving symptoms occured). The authors speculated that the lowering of thalamic activity represents a withdrawal of attention from external sensory stimuli, which may provoke re-experiencing symptoms. It may also be that EP becomes focused on interoceptive, bodily-emotional cues when they feel threatened. Their perception of threat may involve classically conditioned stimuli that tend to reactivate traumatic memories--in which EP are fixed, and implied high arousal levels. Traumatic memories do not involve narratives, but are sensorimotor and highly emotional.

In consert with these findings and hypotheses, our results suggest that as ANP, DID patients are more open to external sensory stimuli than as an EP who is prone to engage in active defense. This would particularly apply when they feel threatened as this EP. Because of ANP's habitual tendency to be numb and depersonalized, they may not have been that alarmed by our instructions to relax, close their eyes, and stay immobile in a loud narrow space. As EP, however, these instructions and conditions may have reminded them of traumatizing circumstances. To cope with the demanding situation, EP may have become focused on subjectively threatening internal cues, implying low thalamus perfusion. At the same time, they may have become self-aware, focused on internally alarming bodily and emotional cues, and prone to reactivate painful memories.

Indeed, comparing EP to ANP in DID patients (DIDep-DIDanp), we found increased rCBF in the primary somatosensory cortex, in several motor-related brain areas, and in the DMPFC (see **Figure 10**). In a number of independent studies, self-referential action was associated with activity in the DMPFC (Gusnard, Akbudak, Shulman, & Raichle, 2001; Kjaer, Nowak, & Lou, 2002; Macrae, Moran, Heatherton, Banfield, & Kelley, 2004). We suggest that in DID patients compared to ANP, EP was attending more to his/her self-state and somatosensory sensations. The primary motor cortex and the premotor cortex are involved in action planning and action execution (Kawashima, Rolland, & O'Sullivan, 1994), and the pre-SMA in the inhibition of motor responses (Neubert & Klein, 2010). Combining these findings, we interpret that as EP, the patients were highly aware of being a body in a threatening situation. This awareness might have triggered a tendency to engage in defense motor reactions, which had to be inhibited in order to be able to fulfill the given resting-state instructions.

In line with our third hypothesis, comparisons of ANP and EP in controls yielded different neural reactivity patterns than comparisons of ANP and EP in DID patients. The actors reported that they used two major strategies to fulfill their simulation task: 1) imagining being another person and 2) trying to experience this other person's feelings. According to cognitive and social neuroscience, the first strategy can be described as visual mental imagery (Kosslyn, Ganis, & Thompson, 2001) and the second as empathizing (Hein & Singer, 2008).

Visual imagery elicits neural activity in visual areas (Kosslyn, et al., 1993; Kosslyn, et al., 2001). The increased perfusion in the occipital pole for controls simulating ANP compared to controls enacting EP (CONanp-CONep) suggests that as ANP, actors particularly engaged in visual imagery. As the participants were requested to keep their eyes closed, activation in occipital areas cannot be explained by visual perception.

The inverse contrast (CONep-CONanp) revealed a higher perfusion in the anterior insula, pars triangularis of the inferior frontal gyrus, frontal operculum, and OFC, which are known to be neural underpinnings of empathy. There are different definitions of empathy in the literature. The second strategy for simulating ANP and EP mentioned above involved empathy in the sense of “Einfühlen”, that is “feeling into someone” (Barnes & Thagard, 1997; Eisenberg & Strayer, 1987). The anterior anterior insula is associated with empathy for pain (Jackson, Meltzoff, & Decety, 2005; Singer, et al., 2004). Pain can occur beyond nociception and can be generalized to mental suffering of any sort (Craig, 2003), such as laying in a scanner as a traumatized anxious (part of a) person. The pars triangularis and the frontal operculum are part of the mirror neuron system (MNS). The main function of the MNS pertains to simulation. For example, observing another person’s actions increases the firing rate of neurons that are also active when we actually perform those actions ourselves (Gallese & Goldman, 1998). Thus, the MNS is involved in understanding the actions and intentions of others (Blakemore & Decety, 2001; Rizzolatti & Craighero, 2004). Neuroimaging studies in autism spectrum disorder patients (Dapretto, et al., 2006) and healthy adults (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003) also suggest that the MNS plays a pivotal role in empathy. Carr et al. (2003) proposed that in concert with the anterior insula, the MNS is involved in grasping the emotional states of others by physically and emotionally feeling what it is like to engage in the observed action. The OFC has been found to be active in empathy tasks as well (Decety & Meyer, 2008; Decety, Michalska, & Akitsuki, 2008; Hynes, Baird, & Grafton, 2006). OFC functioning is critical for social cognition and socially appropriate behavior. Taken together, our data support the idea that DID-simulated controls engaged in envisioning and feeling of what one is not, that is, in simulating ANP and EP.

The study has several limitations. First, although our sample is the largest sample included in an fMRI study to date, it was still relatively small. This was due to the difficulty finding DID patients who are able to alternate between ANP and EP at request and to remain activated, particularly as EP, for a substantial period of time in an fMRI environment. Second, patients who can perform this feat are the ones who have been in treatment for at least several years. Because treatment of DID fosters integration between the different dissociative parts and integration of traumatic memories, studies such as ours are prone to underestimate biopsychosocial differences between these subsystems of the personality in untreated individuals with DID. Another limitation of the study is that only two of our patients were free of medication. Medication washout is not feasible with DID patients. However, it is important to note that medication does not explain the observed differences between ANP and EP in DID.

In conclusion, the current study demonstrates for the first time that in contrast to DID-simulating actors, particularly but not exclusively as EP, DID patients activated brain structures known to be involved in attending self-states, as they responded to relaxation and immobilization instructions in a challenging environment. The study adds to the evidence from supraliminal and subliminal neuroimaging studies of ANP and EP in DID (Hermans, et al., 2006; Reinders, et al., 2003; Reinders, Nijenhuis, et al., 2006; Reinders, et al., 2012; Schlumpf, et al., 2013) that suggestion, role-playing, and fantasy proneness do not explain the disorder. The present study is also the first to show that the examined different prototypes of dissociative parts are associated with different patterns of brain activity when given rest instructions. The findings are consistent with clinical observations and TSDP, but inconsistent with the sociocognitive model of DID.

6. General discussion

6.1. Summary of the results and embedding in the theoretical background

In the following, the most important results of Experiment 1 and Experiment 2 are summarized and embedded in the theoretical background.

6.1.1. Experiment 1

Experiment 1 revealed that as EP, DID patients engage in preconscious perception of angry and neutral faces. Enhanced activity in the brainstem and motor-related areas and the longest RTs in the neutral face condition indicate that EP was aroused by (Jones, 2003) and particularly fixated (Bakvis, et al., 2009; Putman, et al., 2004; Van Honk, et al., 1998, 2000) on neutral faces. EP may regard neutral faces as untrustworthy and threatening, become hypervigilant when confronted with them, and prepare motor defensive reactions. EP is continuously scanning the environment for potential threats, and neutral faces do not express a clear emotion and are therefore not easy to disambiguate. This might be a reason why in EP neutral faces have attracted much preconscious attention. Another explanation is based on findings showing that emotional neglect in childhood is a major predictor of dissociative symptoms in adulthood (Dutra, et al., 2009; Ogawa, et al., 1997). In this context, neutral faces might become an aversively conditioned stimulus for EP, as these faces remind of parental affective unavailability.

In contrast, as ANP, DID patients showed a relative depressed BOLD signal all over the brain in response to subliminally presented angry and neutral faces, suggesting less involvement in these faces. It thus seems that ANP's decreased engagement in consciously perceived trauma-related cues (Reinders, et al., 2003; Reinders, Nijenhuis, et al., 2006) has roots in this dissociative part's reduced preconscious reactivity to trauma-related cues.

Actors were not able to simulate the neural and behavioral reactions observed for ANP and EP in DID. The results of the experiment have major clinical implications in that they show how the disorder can be maintained over decades. EP is the holder of the trauma memory and, therefore, a trauma-related stimulus for ANP. Trauma memories involve aversive sensorimotor and highly emotional experiences that relate

to the traumatic events (Brewin, 2001; Van der Kolk, 1997). In terms of classical conditioning, when ANP is intruded by EP, ANP is exposed to a cluster of unconditioned stimuli, which subsequently can become conditioned fear stimuli. In this context, EP can become a conditioned stimulus for reminders of the terrible events possibly causing ANP to consciously and, in line with our research idea, preconsciously mentally avoid EP. On the other hand, if EP is aware of this rejection, EP may become phobic of the neglectful or rejecting ANP, as neglect is a common precursor of DID (Dutra, et al., 2009; Lyons-Ruth, et al., 2006; Ogawa, et al., 1997). Consequently, EP will tend to fear and avoid ANP as well. The development of a unilateral or bilateral conditioned fear and phobic reactions to each other precludes posttraumatic integration of traumatic memories as well as the integration of ANP and EP (Van der Hart, et al., 2006).

The results also offer suggestions for psychotherapy of trauma-related dissociative disorders. That is, they propose that ANP and EP must be exposed to each other to enhance integration. Furthermore, the clinical findings suggest that therapists of DID patients must be emotionally and behaviorally engaged in order not to trigger and reinforce conditioned emotional and defensive reactions. Therapeutic neutrality will probably scare the patients, particularly as EP, as they may tend to perceive an emotionally neutral therapist as an emotionally unavailable caretaker.

6.1.2. Experiment 2

Previous studies (Hermans, et al., 2006; Reinders, et al., 2003; Reinders, Nijenhuis, et al., 2006) provide insights into dissociative part-dependent reactions to trauma-related stimuli. Experiment 2 extends these findings to a task-free condition. For a DID patient, to relax and lay immobile in a loud narrow brain scanner is, particularly as EP, a challenging and threatening setting. Thus, rest instructions do not imply that DID patients are actually resting. They rather try to deal with the situation of being a self in a threatening situation. The experiment allowed investigation of ANP's and EP's habitual tendencies to deal with threat in a task-free condition. Our data suggest that compared to ANP, as EP, DID patients are self-conscious, body-oriented, and focused in active defense. Furthermore, our data parallel findings demonstrating that the thalamus plays a crucial role in regulating dissociative states (Kim, et al., 2007; Lanius, et al., 2005; Lanius, et al., 2001; Lanius, et al., 2003). Reduced thalamus

activity seems to be related to positive dissociative symptoms (i.e., EP-like symptoms), whereas enhanced thalamic activity is associated with negative dissociative symptoms (i.e., ANP-like symptoms).

The results of the current experiment have not only the potential to increase the understanding of the psychobiology of DID. We also demonstrated that being a genuine DID patient and simulating DID patient are incompatible at the level of neural activity. DID patients followed our rest instructions and elicited a perfusion pattern that is routinely active during rest (default mode activity). In contrast, the actors' perfusion pattern indicates that they engaged in the role-playing task by envisioning (Kosslyn, et al., 2001) being a dissociative part of a DID patient and empathizing his/her feelings (Hein & Singer, 2008).

6.2. Conclusion

In conclusion, the findings of the present dissertation suggest that in DID patients, neural and behavioral reactions in response to masked faces and brain perfusion in a task-free condition are dependent on the type of dissociative part that is dominant during the measurement. Both experiments also demonstrate that actors instructed and motivated to simulate ANP and EP are not able to mimic the neuronal patterns of genuine DID patients. This finding is of major clinical importance because it adds to the evidence that DID is an authentic disorder and cannot be explained by role-playing. The results and interpretations are consistent with clinical observations and the TSDP (Van der Hart, et al., 2006), but contradict the sociocognitive view of DID.

6.3. Implications and directions for future studies

The major aims of the presented experiments were successfully achieved, and the findings give rise to new research questions.

Experiment 1 indicated that trauma leads to alterations in the very early face processing stream. The experiment should be repeated using electro-encephalography (EEG) to benefit from the high temporal resolution in the recording of electrical activity (Jäncke, 2005). In addition, psychophysiological variables, such as heart rate, heart rate variability, and skin conductance, should be assessed.

These peripheral measurements are a useful compliment to fMRI data and help to interpret patterns of arousal and emotionality more concisely.

There are indications that alterations in the default mode network connectivity (i.e. temporal correlation between brain regions) are strongly associated with the pathophysiology of mental disorders (Van den Heuvel & Hulshoff Pol; Whitfield-Gabrieli & Ford, 2012). A functional connectivity analysis is needed to answer the question of whether the functionality of the DMN and its role in self-referential processes is disturbed in DID patients. Additionally, a non-simulating healthy control group should be measured with the same ASL sequence in order to further investigate neural resting-state patterns of DID patients compared to healthy controls and to overcome the paradoxical situation of simulating resting DID patients characterizing the actors.

References

Aguirre, G. K., Detre, J. A., Zarahn, E., & Alsop, D. C. (2002). Experimental design and the relative sensitivity of BOLD and perfusion fMRI. *Neuroimage, 15*(3), 488-500.

Akyuz, G., Dogan, O., Sar, V., Yargic, L. I., & Tutkun, H. (1999). Frequency of dissociative identity disorder in the general population in Turkey. *Compr Psychiatry, 40*(2), 151-159.

Amaral, D. G., Price, J. L., Pitkanen, A., & Carmichael, S. T. (1992). Anatomical organization of primate amygdaloid complex. In W. Aggleton (Ed.), *The Amygdala: Neurobiological Aspects of Emotion, Memory and Mental Dysfunction* (pp. 1-66). New York: Wiley-Liss.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders DSM-IV* (4th ed.). Washington, DC: American Psychiatric Association.

Andreasen, N. C., O'Leary, D. S., Cizadlo, T., Arndt, S., Rezai, K., Watkins, G. L., et al. (1995). Remembering the past: two facets of episodic memory explored with positron emission tomography. *Am J Psychiat, 152*, 1576-1585.

Andrews-Hanna, J. R., Reidler, J. S., Huang, C., & Buckner, R. L. (2010). Evidence for the default network's role in spontaneous cognition. *J Neurophysiol, 104*(1), 322-335.

Armony, J. L., Corbo, V., Clement, M. H., & Brunet, A. (2005). Amygdala response in patients with acute PTSD to masked and unmasked emotional facial expressions. *Am J Psychiatry, 162*(10), 1961-1963.

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *Neuroimage, 26*(3), 839-851.

Bakvis, P., Roelofs, K., Kuyk, J., Edelbroek, P. M., Swinkels, W. A., & Spinhoven, P. (2009). Trauma, stress, and preconscious threat processing in patients with psychogenic nonepileptic seizures. *Epilepsia, 50*(5), 1001-1011.

Barnes, A., & Thagard, P. (1997). Empathy and analogy. *Dialogue Can Philos Rev, 36* 705–720.

Baumgartner, T., Willi, M., & Jancke, L. (2007). Modulation of corticospinal activity by strong emotions evoked by pictures and classical music: a transcranial magnetic stimulation study. *Neuroreport, 18*(3), 261-265.

Benjamin, L. S. (1993). *Interpersonal Diagnosis and Treatment of Personality Disorders* (2 ed.). New York: Guilford.

Bishop, S. J. (2007). Neurocognitive mechanisms of anxiety: an integrative account. *Trends Cogn Sci, 11*(7), 307-316.

Blackford, J. U., Buckholtz, J. W., Avery, S. N., & Zald, D. H. (2010). A unique role for the human amygdala in novelty detection. *Neuroimage, 50*(3), 1188-1193.

Blakemore, S. J., & Decety, J. (2001). From the perception of action to the understanding of intention. *Nat Rev Neurosci, 2*(8), 561-567.

Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., et al. (1996). Response and habituation of the human amygdala during visual processing of facial expression. *Neuron, 17*(5), 875-887.

Bremner, J. D., Narayan, M., Staib, L. H., Southwick, S. M., McGlashan, T., & Charney, D. S. (1999). Neural correlates of memories of childhood sexual

abuse in women with and without posttraumatic stress disorder. *Am J Psychiatry, 156*(11), 1787-1795.
Bremner, J. D., Staib, L. H., Kaloupek, D., Southwick, S. M., Soufer, R., & Charney, D. S. (1999). Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. *Biol Psychiatry, 45*(7), 806-816.
Brewin, C. R. (2001). A cognitive neuroscience account of posttraumatic stress disorder and its treatment. *Behav Res Ther, 39*(4), 373-393.
Brühl, A. B., Rufer, M., Delsignore, A., Kaffenberger, T., Jancke, L., & Herwig, U. (2011). Neural correlates of altered general emotion processing in social anxiety disorder. *Brain Res, 1378*, 72-83.
Bryant, R. A., Kemp, A. H., Felmingham, K. L., Liddell, B., Olivieri, G., Peduto, A., et al. (2008). Enhanced amygdala and medial prefrontal activation during nonconscious processing of fear in posttraumatic stress disorder: an fMRI study. *Hum Brain Mapp, 29*(5), 517-523.
Büchel, C., Morris, J., Dolan, R. J., & Friston, K. J. (1998). Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron, 20*(5), 947-957.
Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci, 1124*, 1-38.
Buxton, R. B. (2002). *Introducing to Functional Magnetic Resonance Imaging*. Cambridge, UK: Cambridge University Press.
Carr, L., Iacoboni, M., Dubeau, M. C., Mazziotta, J. C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci U S A, 100*(9), 5497-5502.
Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain, 129*(Pt 3), 564-583.
Cheesman, J., & Merikle, P. M. (1984). Priming with and without awareness. *Percept Psychophys, 36*, 387-395.
Christoff, K., Gordon, A. M., Smallwood, J., Smith, R., & Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proc Natl Acad Sci U S A, 106*(21), 8719-8724.
Cisler, J. M., & Koster, E. H. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clin Psychol Rev, 30*(2), 203-216.
Coons, P. M., Milstein, V., & Marley, C. (1982). EEG studies of two multiple personalities and a control. *Arch Gen Psychiatry, 39*(7), 823-825.
Craig, A. D. (2003). Pain mechanisms: labeled lines versus convergence in central processing. *Annu Rev Neurosci, 26*, 1-30.
D'Esposito, M., Deouell, L. Y., & Gazzaley, A. (2003). Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. *Nat Rev Neurosci, 4*(11), 863-872.
Dalenberg, C. J., Brand, B. L., Gleaves, D. H., Dorahy, M. J., Loewenstein, R. J., Cardena, E., et al. (2012). Evaluation of the evidence for the trauma and fantasy models of dissociation. *Psychol Bull, 138*(3), 550-588.
Dapretto, M., Davies, M. S., Pfeifer, J. H., Scott, A. A., Sigman, M., Bookheimer, S. Y., et al. (2006). Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. *Nat Neurosci, 9*(1), 28-30.

Davis, M., & Whalen, P. J. (2001). The amygdala: vigilance and emotion. *Mol Psychiatry, 6*(1), 13-34.
Decety, J., & Meyer, M. (2008). From emotion resonance to empathic understanding: a social developmental neuroscience account. *Dev Psychopathol, 20*(4), 1053-1080.
Decety, J., Michalska, K. J., & Akitsuki, Y. (2008). Who caused the pain? An fMRI investigation of empathy and intentionality in children. *Neuropsychologia, 46*(11), 2607-2614.
Dell, P. F. (2006). A new model of dissociative identity disorder. *Psychiatr Clin North Am, 29*(1), 1-26, vii.
Dell, P. F., & O'Neil, J. A. (2009). Prefrace. In P. F. Dell & J. A. O'Neil (Eds.), *Dissociation and the Dissociative Disorders: DSM-V and Beyond* (pp. xix-xxi). New York: Routledge.
Desikan, R. S., Segonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., et al. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage, 31*(3), 968-980.
Detre, J. A., Rao, H., Wang, D. J., Chen, Y. F., & Wang, Z. (2012). Applications of arterial spin labeled MRI in the brain. *J Magn Reson Imaging, 35*(5), 1026-1037.
Detre, J. A., Zhang, W., Roberts, D. A., Silva, A. C., Williams, D. S., Grandis, D. J., et al. (1994). Tissue specific perfusion imaging using arterial spin labeling. *NMR Biomed, 7*(1-2), 75-82.
Diseth, T. H. (2006). Dissociation following traumatic medical treatment procedures in childhood: a longitudinal follow-up. *Dev Psychopathol, 18*(1), 233-251.
Donegan, N. H., Sanislow, C. A., Blumberg, H. P., Fulbright, R. K., Lacadie, C., Skudlarski, P., et al. (2003). Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. *Biol Psychiatry, 54*(11), 1284-1293.
Dutra, L., Bureau, J. F., Holmes, B., Lyubchik, A., & Lyons-Ruth, K. (2009). Quality of early care and childhood trauma: a prospective study of developmental pathways to dissociation. *J Nerv Ment Dis, 197*(6), 383-390.
Ehlers, A., Steil, R., Winter, H., & Foa, E. B. (1996). *Deutsche Übersetzung der Posttraumatic Diagnostic Scale (PDS)*. Oxford: University, Warneford Hospital.
Eisenberg, N., & Strayer, J. (1987). Critical issues in the study of empathy. In N. Eisenberg & J. Strayer (Eds.), *Empathy and its Development* (pp. 3-13). New York: Cambridge University Press.
Ellason, J. W., Ross, C. A., & Fuchs, D. L. (1996). Lifetime axis I and II comorbidity and childhood trauma history in dissociative identity disorder. *Psychiatry, 59*(3), 255-266.
Eysenck, M. W., Mogg, K., May, J., Richards, A., & Mathews, A. (1991). Bias in interpretation of ambiguous sentences related to threat in anxiety. *J Abnorm Psychol, 100*(2), 144-150.
Felmingham, K., Kemp, A. H., Williams, L., Falconer, E., Olivieri, G., Peduto, A., et al. (2008). Dissociative responses to conscious and non-conscious fear impact underlying brain function in post-traumatic stress disorder. *Psychol Med, 38*(12), 1771-1780.
Fink, G. R., Markowitsch, H. J., Reinkemeier, M., Bruckbauer, T., Kessler, J., & Heiss, W. D. (1996). Cerebral representation of one's own past: neural

networks involved in autobiographical memory. *J Neurosci, 16*(13), 4275-4282.

Fischer, H., Wright, C. I., Whalen, P. J., McInerney, S. C., Shin, L. M., & Rauch, S. L. (2003). Brain habituation during repeated exposure to fearful and neutral faces: a functional MRI study. *Brain Res Bull, 59*(5), 387-392.

Foote, B., Smolin, Y., Kaplan, M., Legatt, M. E., & Lipschitz, D. (2006). Prevalence of dissociative disorders in psychiatric outpatients. *Am J Psychiatry, 163*(4), 623-629.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A, 102*(27), 9673-9678.

Fox, P. T., & Raichle, M. E. (1986). Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci U S A, 83*(4), 1140-1144.

Fransson, P. (2005). Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. *Hum Brain Mapp, 26*(1), 15-29.

Friedl, M. C., & Draijer, N. (2000). Dissociative disorders in Dutch psychiatric inpatients. *Am J Psychiatry, 157*(6), 1012-1013.

Friston, K. J., Holmes, A., Poline, J. B., Price, C. J., & Frith, C. D. (1996). Detecting activations in PET and fMRI: levels of inference and power. *Neuroimage, 4*(3 Pt 1), 223-235.

Friston, K. J., Worsley, K. J., Frackowiak, R. S. J., Mazziotta, J. C., & Evans, A. C. (1994). Assessing the significance of focal activations using their spatial extent. *Hum Brain Mapp, 1*, 210-220.

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., et al. (2009). Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *J Psychiatry Neurosci, 34*(6), 418-432.

Galbraith, P. M., & Neubauer, P. J. (2000). Underwriting considerations for dissociative disorders. *J Insur Med, 32*(2), 71-78.

Gallese, V., & Goldman, A. (1998). Mirror neurons and the simulation theory of mind-reading. *Trends Cogn Sci, 2*(12), 493-501.

Gast, U., Hofmann, A., Oswald, T., & Zündorf, F. (2000). *Das Strukturierte Klinische Interview für DSM-IV Dissoziative Störungen (SKID-D). Deutsche Fassung. Manual und Interviewheft*. Göttingen: Hogrefe.

Gast, U., Rodewald, F., Nickel, V., & Emrich, H. M. (2001). Prevalence of dissociative disorders among psychiatric inpatients in a German university clinic. *J Nerv Ment Dis, 189*(4), 249-257.

Gevers, S., Van Osch, M. J., Bokkers, R. P., Kies, D. A., Teeuwisse, W. M., Majoie, C. B., et al. (2011). Intra- and multicenter reproducibility of pulsed, continuous and pseudo-continuous arterial spin labeling methods for measuring cerebral perfusion. *J Cereb Blood Flow Metab, 31*(8), 1706-1715.

Giesbrecht, T., Lynn, S. J., Lilienfeld, S. O., & Merckelbach, H. (2008). Cognitive processes in dissociation: An analysis of core theoretical assumptions. *Psychol Bull, 134*, 617-647.

Gleaves, D. H. (1996). The sociocognitive model of dissociative identity disorder: a reexamination of the evidence. *Psychol Bull, 120*(1), 42-59.

Gorno-Tempini, M. L., Pradelli, S., Serafini, M., Pagnoni, G., Baraldi, P., Porro, C., et al. (2001). Explicit and incidental facial expression processing: an fMRI study. *Neuroimage, 14*(2), 465-473.

Greenwald, A. G., Draine, S. C., & Abrams, R. L. (1996). Semantic activation without conscious identification in dichotic listening, parafoveal vision, and visual masking: A survey and appraisal. *Science, 273*, 1699-1702.

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A, 100*(1), 253-258.

Greicius, M. D., & Menon, V. (2004). Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. *J Cogn Neurosci, 16*(9), 1484-1492.

Grillon, C., Lissek, S., Rabin, S., McDowell, D., Dvir, S., & Pine, D. S. (2008). Increased anxiety during anticipation of unpredictable but not predictable aversive stimuli as a psychophysiologic marker of panic disorder. *Am J Psychiatry, 165*(7), 898-904.

Gusnard, D. A., Akbudak, E., Shulman, G. L., & Raichle, M. E. (2001). Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci U S A, 98*(7), 4259-4264.

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci, 2*(10), 685-694.

Hajcak, G., Molnar, C., George, M. S., Bolger, K., Koola, J., & Nahas, Z. (2007). Emotion facilitates action: a transcranial magnetic stimulation study of motor cortex excitability during picture viewing. *Psychophysiology, 44*(1), 91-97.

Hautzinger, M., Keller, F., & Kühner, C. (2006). *Beck Depressions-Inventar (BDI-II). Revision*. Frankfurt a. M.: Harcourt Test Services.

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends Cogn Sci, 4*(6), 223-233.

Hein, G., & Singer, T. (2008). I feel how you feel but not always: the empathic brain and its modulation. *Curr Opin Neurobiol, 18*(2), 153-158.

Hendler, T., Rotshtein, P., Yeshurun, Y., Weizmann, T., Kahn, I., Ben-Bashat, D., et al. (2003). Sensing the invisible: differential sensitivity of visual cortex and amygdala to traumatic context. *Neuroimage, 19*(3), 587-600.

Henke, K., Landis, T., & Markowitsch, H. J. (1994). Subliminal perception of words and faces. *Int J Neurosci, 75*(3-4), 181-187.

Henke, K., Mondadori, C. R., Treyer, V., Nitsch, R. M., Buck, A., & Hock, C. (2003). Nonconscious formation and reactivation of semantic associations by way of the medial temporal lobe. *Neuropsychologia, 41*(8), 863-876.

Henke, K., Treyer, V., Nagy, E. T., Kneifel, S., Dursteler, M., Nitsch, R. M., et al. (2003). Active hippocampus during nonconscious memories. *Conscious Cogn, 12*(1), 31-48.

Hermans, E. J., Nijenhuis, E. R., Van Honk, J., Huntjens, R. J., & Van der Hart, O. (2006). Identity state-dependent attentional bias for facial threat in dissociative identity disorder. *Psychiatry Res, 141*(2), 233-236.

Holaway, R. M., Heimberg, R. G., & Coles, M. E. (2006). A comparison of intolerance of uncertainty in analogue obsessive-compulsive disorder and generalized anxiety disorder. *J Anxiety Disord, 20*(2), 158-174.

Holender, D. (1986). Semantic activation without conscious identification in dichotic listening, parafoveal vision, and visual masking: A survey and appraisal. *Behav Brain Sci, 9*, 1-23.

Hughes, J. R., Kuhlman, D. T., Fichtner, C. G., & Gruenfeld, M. J. (1990). Brain mapping in a case of multiple personality. *Clin Electroencephalogr, 21*(4), 200-209.

Hynes, C. A., Baird, A. A., & Grafton, S. T. (2006). Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. *Neuropsychologia, 44*(3), 374-383.

ISSD (1997). *Guidlines for Treating Dissociative Identity Disorder (Multiple Personality) in Adults*. Chicago: Author.

Jackson, P. L., Meltzoff, A. N., & Decety, J. (2005). How do we perceive the pain of others? A window into the neural processes involved in empathy. *Neuroimage, 24*(3), 771-779.

Jäncke, L. (2005). *Methoden der Bildgebung in der Psychologie und den kognitiven Neurowissenschaften*. Stuttgart: Kohlhammer.

Johnson, J. G., Cohen, P., Kasen, S., & Brook, J. S. (2006). Dissociative disorders among adults in the community, impaired functioning, and axis I and II comorbidity. *J Psychiatr Res, 40*(2), 131-140.

Jones, B. E. (2003). Arousal systems. *Front Biosci, 8*, s438-451.

Kawashima, R., Rolland, P. E., & O'Sullivan, B. T. (1994). Fields in human motor areas involved in preparation for reaching, actual reaching, and visumotor learning: A positron emission tomography study. *J Neurosci, 14*(6), 3462-3474.

Kelley, W. M., Macrae, C. N., Wyland, C. L., Caglar, S., Inati, S., & Heatherton, T. F. (2002). Finding the self? An event-related fMRI study. *J Cogn Neurosci, 14*(5), 785-794.

Kihlstrom, J. F., Barnhardt, T. M., & Tataryn, D. J. (1992). Implicit perception. In R. F. Bornstein & T. S. Pittman (Eds.), *Perception Without Awareness: Cognitive, Clinical, and Social Perspectives* (pp. 17-54). New York: Guilford Press.

Kim, S. J., Lyoo, I. K., Lee, Y. S., Kim, J., Sim, M. E., Bae, S. J., et al. (2007). Decreased cerebral blood flow of thalamus in PTSD patients as a strategy to reduce re-experience symptoms. *Acta Psychiatr Scand, 116*(2), 145-153.

Kjaer, T. W., Nowak, M., & Lou, H. C. (2002). Reflective self-awareness and conscious states: PET evidence for a common midline parietofrontal core. *Neuroimage, 17*(2), 1080-1086.

Korol, S. (2008). Familial and social support as protective factors against the development of dissociative identity disorder. *J Trauma Dissociation, 9*(2), 249-267.

Kosslyn, S. M., Alpert, N. M., Thomson, W. L., Maljkovic, V., Weise, S. B., Chabris, C. F., et al. (1993). Visual mental imagery activates topographically organized visual cortex: PET investigations. *J Cogn Neurosci, 5*, 635-642.

Kosslyn, S. M., Ganis, G., & Thompson, W. L. (2001). Neural foundations of imagery. *Nat Rev Neurosci, 2*(9), 635-642.

Krystal, J. H., Bennett, A. L., Bremner, J. D., Southwitck, S. M., & Charney, D. S. (1995). Toward a cognitive neuroscience of dissociation and altered memory functions in posttraumatic stress disorder. In F. M. J., D. S. Charney & A. Y. Deutsch (Eds.), *Neurobiological and Clinical Consequences of Stress: From Normal Adaptions to PTSD* (pp. 239-268). New York: Raven Press.

Lanius, R. A., Bluhm, R., Lanius, U., & Pain, C. (2006). A review of neuroimaging studies in PTSD: heterogeneity of response to symptom provocation. *J Psychiatr Res, 40*(8), 709-729.

Lanius, R. A., Williamson, P. C., Bluhm, R. L., Densmore, M., Boksman, K., Neufeld, R. W., et al. (2005). Functional connectivity of dissociative responses in posttraumatic stress disorder: a functional magnetic resonance imaging investigation. *Biol Psychiatry, 57*(8), 873-884.

Lanius, R. A., Williamson, P. C., Boksman, K., Densmore, M., Gupta, M., Neufeld, R. W., et al. (2002). Brain activation during script-driven imagery induced dissociative responses in PTSD: a functional magnetic resonance imaging investigation. *Biol Psychiatry, 52*(4), 305-311.

Lanius, R. A., Williamson, P. C., Densmore, M., Boksman, K., Gupta, M. A., Neufeld, R. W., et al. (2001). Neural correlates of traumatic memories in posttraumatic stress disorder: a functional MRI investigation. *Am J Psychiatry, 158*(11), 1920-1922.

Lanius, R. A., Williamson, P. C., Hopper, J., Densmore, M., Boksman, K., Gupta, M. A., et al. (2003). Recall of emotional states in posttraumatic stress disorder: an fMRI investigation. *Biol Psychiatry, 53*(3), 204-210.

Laux, L., Glanzmann, P., Schaffner, P., & Spielberger, C. D. (1981). *Das State-Trait-Angstinventar. Theoretische Grundlagen und Handanweisung*. Weinheim: Beltz Test GmbH.

LeDoux, J. E. (1998). *The Emotional Brain: The Mysterious Underpinnings of Emotional Life*. New York: Touchstone.

Lewis, D. O., Yeager, C. A., Swica, Y., Pincus, J. H., & Lewis, M. (1997). Objective documentation of child abuse and dissociation in 12 murderers with dissociative identity disorder. *Am J Psychiatry, 154*(12), 1703-1710.

Lilienfeld, S. O., Lynn, S. J., Kirsch, I., Chaves, J. F., Sarbin, T. R., Ganaway, G. K., et al. (1999). Dissociative identity disorder and the sociocognitive model: recalling the lessons of the past. *Psychol Bull, 125*(5), 507-523.

Linehan, M. M. (1993). *Cognitive-behavioral Treatment of Borderline Personality Disorder*. New York, N.Y.: Guilford Press.

Liu, T. T., & Brown, G. G. (2007). Measurement of cerebral perfusion with arterial spin labeling: Part 1. Methods. *J Int Neuropsychol Soc, 13*(3), 517-525.

Loftus, E. F., Coan, J., & Pickrell, J. E. (1996). Manufacturing false memories using bits of reality. In L. Reder (Ed.), *Implicit Memory and Metacognition*. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.

Loftus, E. F., & Ketcham, K. (1994). *The Myth of Repressed Memory*. New York: St. Martin's Press.

Loftus, E. F., & Pickrell, J. E. (1995). The formation of false memories. *Psychiat Ann, 25*, 720-725.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature, 412*(6843), 150-157.

Lundquist, D., Flykt, A., & Öhman, A. (1998). *The Karolinska Directed Emotional Faces - KDEF, CD ROM from Department of Clinical Neuroscience, Psychology section, Karolinska Institute, ISBN 91-630-7164-9.*

Lynn, S. J., Lilienfeld, S. O., Merckelbach, H., Giesbrecht, T., & Van der Kloet, D. (2012). Dissociation and dissociative disorders: challenging conventional wisdom. *Curr Dir Psychol Sci, 21*(48), 48-53.

Lyons-Ruth, K., Dutra, L., Schuder, M., & Bianchi, I. (2006). From infant attachment disorganization to adult dissociation: Relational adaptations or traumatic experiences? In R. Chevetz (Ed.), *Dissociative Disorders* (Vol. 29, pp. 63-86). Psychiatric Clinics of North America.

Macrae, C. N., Moran, J. M., Heatherton, T. F., Banfield, J. F., & Kelley, W. M. (2004). Medial prefrontal activity predicts memory for self. *Cereb Cortex, 14*(6), 647-654.

Malonek, D., & Grinvald, A. (1996). Interactions between electrical activity and cortical microcirculation revealed by imaging spectroscopy: implications for functional brain mapping. *Science, 272*(5261), 551-554.

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: the default network and stimulus-independent thought. *Science, 315*(5810), 393-395.

Mazoyer, B., Zago, L., Mellet, E., Bricogne, S., Etard, O., Houde, O., et al. (2001). Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Res Bull, 54*(3), 287-298.

Merckelbach, H., à Campo, J., Hardy, S., & Giesbrecht, T. (2005). Dissociation and fantasy proneness in psychiatric patients: a preliminary study. *Compr Psychiatry, 46*(3), 181-185.

Merckelbach, H., Devilly, G. J., & Rassin, E. (2002). Alters in dissociative identity disorder. Metaphors or genuine entities? *Clin Psychol Rev, 22*(4), 481-497.

Merckelbach, H., Horselenberg, R., & Schmidt, H. (2002). Modeling the connection between self-reported trauma and dissociation in a student sample. *Pers Indiv Differ, 32*, 695-705.

Merckelbach, H., & Muris, P. (2001). The causal link between self-reported trauma and dissociation: a critical review. *Behav Res Ther, 39*(3), 245-254.

Merckelbach, H., Muris, P., Rassin, E., & Horselenberg, R. (2000). Dissociative experiences and interrogative suggestibility in college students. *Pers Indiv Differ, 29*, 1133-1140.

Merckelbach, H., Rassin, E., & Muris, P. (2000). Dissociation, schizotypy, and fantasy proneness in undergraduate students. *J Nerv Ment Dis, 188*(7), 428-431.

Merskey, H. (1992). The manufacture of personalities. The production of multiple personality disorder. *Br J Psychiatry, 160*, 327-340.

Mesman, J., Van IJzendoorn, M. H., & Bakermans-Kranenburg, M. J. (2009). The many faces of the Still-Face Paradigm: A review and meta-analysis. *Dev Rev, 29*, 120-162.

Metzinger, T. (2003). *Being No One: The Self-Model Theory of Subjectivity*. Cambridge, MA: MIT Press.

Morris, J. S., Ohman, A., & Dolan, R. J. (1998). Conscious and unconscious emotional learning in the human amygdala. *Nature, 393*(6684), 467-470.

Nakamura, K., Kawashima, R., Sato, N., Nakamura, A., Sugiura, M., Kato, T., et al. (2000). Functional delineation of the human occipito-temporal areas related to face and scene processing. A PET study. *Brain, 123 (Pt 9)*, 1903-1912.

Neubert, F. X., & Klein, M. C. (2010). What is driving inhibition-related activity in the frontal lobe? *J Neurosci, 30*(14), 4830-4832.

Nijenhuis, E. R., & Van der Hart, O. (2011). Dissociation in trauma: a new definition and comparison with previous formulations. *J Trauma Dissociation, 12*(4), 416-445.

Nijenhuis, E. R. S. (2004). *Somatoform Dissociation: Phenomena, Measurement, and Theoretical Issues*. New York: Norton.

Nijenhuis, E. R. S., & Den Boer, J. A. (2009). Psychobiology of traumatisation and trauma-related structural dissociation of the personality. In P. F. Dell & J. A. O'Neil (Eds.), *Dissociation and the Dissociative Disorders: DSM-V and Beyond* (pp. 337-367). New York: Routledge.

Nijenhuis, E. R. S., Van der Hart, O., & Steele, K. (2002). The emerging psychobiology of trauma-related dissociation and dissociative disorders. In H. D'Haenen, J. A. Den Boer & P. Willner (Eds.), *Biological Psychiatry* (pp. 1079-1098). London: Wiley.

Nijenhuis, E. R. S., Van der Hart, O., & Steele, K. (2004). Strukturelle Dissoziation der Persönlichkeitsstruktur, traumatischer Ursprung, phobische Residuen. In L. Reddemann, A. Hofmann & U. Gast (Eds.), *Psychotherapie der dissoziativen Störungen* (pp. 47-69). Stuttgart: Thieme.

Nitschke, J. B., Sarinopoulos, I., Oathes, D. J., Johnstone, T., Whalen, P. J., Davidson, R. J., et al. (2009). Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response. *Am J Psychiatry, 166*(3), 302-310.

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006). Self-referential processing in our brain--a meta-analysis of imaging studies on the self. *Neuroimage, 31*(1), 440-457.

Ogawa, J. R., Sroufe, L. A., Weinfield, N. S., Carlson, E. A., & Egeland, B. (1997). Development and the fragmented self: longitudinal study of dissociative symptomatology in a nonclinical sample. *Dev Psychopathol, 9*(4), 855-879.

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A, 87*(24), 9868-9872.

Ogawa, S., Menon, R. S., Tank, D. W., Kim, S. G., Merkle, H., Ellermann, J. M., et al. (1993). Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. *Biophys J, 64*(3), 803-812.

Öhman, A. (2002). Automaticity and the amygdala: Nonconscious response to emotional faces. *Curr Dir Psychol Sci, 11*, 62-66.

Öhman, A. (2005). The role of the amygdala in human fear: automatic detection of threat. *Psychoneuroendocrinology, 30*(10), 953-958.

Öhman, A., & Soares, J. J. (1994). "Unconscious anxiety": phobic responses to masked stimuli. *J Abnorm Psychol, 103*(2), 231-240.

Oliveri, M., Babiloni, C., Filippi, M. M., Caltagirone, C., Babiloni, F., Cicinelli, P., et al. (2003). Influence of the supplementary motor area on primary motor cortex excitability during movements triggered by neutral or emotionally unpleasant visual cues. *Exp Brain Res, 149*(2), 214-221.

Osuch, E. A., Benson, B., Geraci, M., Podell, D., Herscovitch, P., McCann, U. D., et al. (2001). Regional cerebral blood flow correlated with flashback intensity in patients with posttraumatic stress disorder. *Biol Psychiatry, 50*(4), 246-253.

Pauling, L., & Coryell, C. D. (1936). The Magnetic Properties and Structure of the Hemochromogens and Related Substances. *Proc Natl Acad Sci U S A, 22*(3), 159-163.

Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage, 16*(2), 331-348.

Phelps, E. A., O'Connor, K. J., Gatenby, J. C., Gore, J. C., Grillon, C., & Davis, M. (2001). Activation of the left amygdala to a cognitive representation of fear. *Nat Neurosci, 4*(4), 437-441.

Piper, A., & Merskey, H. (2004). The persistence of folly: A critical examination of dissociative identity disorder. Part I. The excesses of an improbable concept. *Canadian Journal of Psychiatry, 49*, 592-600.

Pitcher, D., Walsh, V., Yovel, G., & Duchaine, B. (2007). TMS evidence for the involvement of the right occipital face area in early face processing. *Curr Biol, 17*(18), 1568-1573.

Price, C. J., & Friston, K. J. (1997). Cognitive conjunction: a new approach to brain activation experiments. *Neuroimage, 5*(4 Pt 1), 261-270.

Price, C. J., Moore, C. J., & Friston, K. J. (1997). Subtractions, conjunctions, and interactions in experimental design of activation studies. *Hum Brain Mapp, 5*(4), 264-272.

Putman, P., Hermans, E., & Van Honk, J. (2004). Emotional stroop performance for masked angry faces: it's BAS, not BIS. *Emotion, 4*(3), 305-311.

Putnam, F. W. (1997). *Dissociation in Children and Adolescents: A Developmental Perspective*. New York: Guilford Press.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proc Natl Acad Sci U S A, 98*(2), 676-682.

Raichle, M. E., & Snyder, A. Z. (2007). A default mode of brain function: a brief history of an evolving idea. *Neuroimage, 37*(4), 1083-1090; discussion 1097-1089.

Rainer, G., Augath, M., Trinath, T., & Logothetis, N. K. (2001). Nonmonotonic noise tuning of BOLD fMRI signal to natural images in the visual cortex of the anesthetized monkey. *Curr Biol, 11*(11), 846-854.

Rauch, S. L., Van der Kolk, B. A., Fisler, R. E., Alpert, N. M., Orr, S. P., Savage, C. R., et al. (1996). A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Arch Gen Psychiatry, 53*(5), 380-387.

Rauch, S. L., Whalen, P. J., Shin, L. M., McInerney, S. C., Macklin, M. L., Lasko, N. B., et al. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biol Psychiatry, 47*(9), 769-776.

Reinders, A. A. T. S., Den Boer, J. A., & Buchel, C. (2005). The robustness of perception. *Eur J Neurosci, 22*(2), 524-530.

Reinders, A. A. T. S., Glascher, J., De Jong, J. R., Willemsen, A. T., Den Boer, J. A., & Buchel, C. (2006). Detecting fearful and neutral faces: BOLD latency differences in amygdala-hippocampal junction. *Neuroimage, 33*(2), 805-814.

Reinders, A. A. T. S., Nijenhuis, E. R. S., Paans, A. M., Korf, J., Willemsen, A. T., & Den Boer, J. A. (2003). One brain, two selves. *Neuroimage, 20*(4), 2119-2125.

Reinders, A. A. T. S., Nijenhuis, E. R. S., Quak, J., Korf, J., Haaksma, J., Paans, A. M., et al. (2006). Psychobiological characteristics of dissociative identity disorder: a symptom provocation study. *Biol Psychiatry, 60*(7), 730-740.

Reinders, A. A. T. S., Willemsen, A. T. M., Vos, H. P. J., Den Boer, J. A., & Nijenhuis, E. R. S. (2012). Fact or factitious? A psychobiological study of authentic and simulated dissociative identity states. *PLoS One, 6*(7), e39279.

Rifkin, A., Ghisalbert, D., Dimatou, S., Jin, C., & Sethi, M. (1998). Dissociative identity disorder in psychiatric inpatients. *Am J Psychiatry, 155*(6), 844-845.

Rizzolatti, G., & Craighero, L. (2004). The mirror-neuron system. *Annu Rev Neurosci, 27*, 169-192.

Rolls, E. T., Tovee, M. J., & Panzeri, S. (1999). The neurophysiology of backward visual masking: information analysis. *J Cogn Neurosci, 11*(3), 300-311.

Sakamoto, H., Fukuda, R., Okuaki, T., Rogers, M., Kasai, K., Machida, T., et al. (2005). Parahippocampal activation evoked by masked traumatic images in posttraumatic stress disorder: a functional MRI study. *Neuroimage, 26*(3), 813-821.

Sander, D., Grafman, J., & Zalla, T. (2003). The human amygdala: an evolved system for relevance detection. *Rev Neurosci, 14*(4), 303-316.

Sar, V., Akyuz, G., & Dogan, O. (2007). Prevalence of dissociative disorders among women in the general population. *Psychiatry Res, 149*(1-3), 169-176.

Sar, V., Unal, S. N., Kiziltan, E., Kundakci, T., & Ozturk, E. (2001). HMPAO SPECT study of regional cerebral blood flow in dissociative identity disorder. *J Trauma Dissociation, 2*(2), 5-25.

Schlumpf, Y. R., Nijenhuis, E. R. S., Chalavi, S., Weder, E. V., Zimmermann, E., Lüchinger, R., et al. (2013). Dissociative part-dependent biopsychosocial reactions to backward masked angry and neutral faces: An fMRI study of dissociative identity disorder. *Neuroimage: Clinical, 3*, 54-64.

Schuff, N., Zhang, Y., Zhan, W., Lenoci, M., Ching, C., Boreta, L., et al. (2011). Patterns of altered cortical perfusion and diminished subcortical integrity in posttraumatic stress disorder: an MRI study. *Neuroimage, 54 Suppl 1*, S62-68.

Schwartz, C. E., Wright, C. I., Shin, L. M., Kagan, J., Whalen, P. J., McMullin, K. G., et al. (2003). Differential amygdalar response to novel versus newly familiar neutral faces: a functional MRI probe developed for studying inhibited temperament. *Biol Psychiatry, 53*(10), 854-862.

Shin, L. M., Kosslyn, S. M., McNally, R. J., Alpert, N. M., Thompson, W. L., Rauch, S. L., et al. (1997). Visual imagery and perception in posttraumatic stress disorder. A positron emission tomographic investigation. *Arch Gen Psychiatry, 54*(3), 233-241.

Shin, L. M., McNally, R. J., Kosslyn, S. M., Thompson, W. L., Rauch, S. L., Alpert, N. M., et al. (1999). Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: A PET investigation. *Am J Psychiatry, 156*(4), 575-584.

Shin, L. M., Orr, S. P., Carson, M. A., Rauch, S. L., Macklin, M. L., Lasko, N. B., et al. (2004). Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Arch Gen Psychiatry, 61*(2), 168-176.

Shin, L. M., Whalen, P. J., Pitman, R. K., Bush, G., Macklin, M. L., Lasko, N. B., et al. (2001). An fMRI study of anterior cingulate function in posttraumatic stress disorder. *Biol Psychiatry, 50*(12), 932-942.

Shulman, G. L., Fiez, J. A., Corbetta, M., Buckner, R. L., Miezin, F. M., Raichle, M. E., et al. (1997). Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. *J Cogn Neurosci, 9*, 648-663.

Simeon, D., Guralnik, O., Hazlett, E. A., Spiegel-Cohen, J., Hollander, E., & Buchsbaum, M. S. (2000). Feeling unreal: a PET study of depersonalization disorder. *Am J Psychiatry, 157*(11), 1782-1788.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R. J., & Frith, C. D. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science, 303*(5661), 1157-1162.

Spanos, N. P. (1994). Multiple identity enactments and multiple personality disorder: A sociocognitive perspective. *Psychol Bull, 116*(1), 143-165.

Spanos, N. P. (1996). Multiple Identities and False Memories: A Sociocognitive Perspective. Washington, D.C.: American Psychological Association.

Steele, K., Van der Hart, O., & Nijenhuis, E. R. (2005). Phase-oriented treatment of structural dissociation in complex traumatization: overcoming trauma-related phobias. *J Trauma Dissociation, 6*(3), 11-53.

Steinberg, M. (1993). *Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D)*. Washington, DC: American Psychiatric Press.

Svoboda, E., McKinnon, M. C., & Levine, B. (2006). The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia, 44*(12), 2189-2208.

Thulborn, K. R., Waterton, J. C., Matthews, P. M., & Radda, G. K. (1982). Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. *Biochim Biophys Acta, 714*(2), 265-270.

Tian, L., Jiang, T., Liu, Y., Yu, C., Wang, K., Zhou, Y., et al. (2007). The relationship within and between the extrinsic and intrinsic systems indicated by resting state correlational patterns of sensory cortices. *Neuroimage, 36*(3), 684-690.

Tjandra, T., Brooks, J. C., Figueiredo, P., Wise, R., Matthews, P. M., & Tracey, I. (2005). Quantitative assessment of the reproducibility of functional activation measured with BOLD and MR perfusion imaging: implications for clinical trial design. *Neuroimage, 27*(2), 393-401.

Trickett, P. K., Noll, J. G., & Putnam, F. W. (2011). The impact of sexual abuse on female development: lessons from a multigenerational, longitudinal research study. *Dev Psychophathol, 23*, 453–476

Tronick, E., Als, H., Adamson, L., Wise, S., & Brazelton, T. B. (1978). The infant's response to entrapment between contradictory messages in face-to-face interaction. *J Am Acad Child Psychiatry, 17*(1), 1-13.

Tulving, E., Kapur, S., Craik, F. I., Moscovitch, M., & Houle, S. (1994). Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. *Proc Natl Acad Sci U S A, 91*(6), 2016-2020.

Tutkun, H., Sar, V., Yargic, L. I., Ozpulat, T., Yanik, M., & Kiziltan, E. (1998). Frequency of dissociative disorders among psychiatric inpatients in a Turkish University Clinic. *Am J Psychiatry, 155*(6), 800-805.

Van Balen, L. (2005). *Activation and localization of the emotional circuits in the brain: an fMRI study in patients with schizophrenia and healthy volunteers.* Unpublished Master thesis, Rijksuniversiteit Groningen, Groningen.

Van den Heuvel, M. P., & Hulshoff Pol, H. E. (2010). Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur Neuropsychopharmacol, 20*(8), 519-534.

Van der Hart, O., Nijenhuis, E. R. S., & Steele, K. (2006). *The Haunted Self: Structural Dissociation and the Treatment of Chronic Traumatization*. New York: W.W. Norton & Company.

Van der Kolk, B. A. (1997). The psychobiology of posttraumatic stress disorder. *J Clin Psychiatry, 58 Suppl 9*, 16-24.

Van Honk, J., Tuiten, A., Van den Hout, M., Koppeschaar, H., Thijssen, J., De Haan, E., et al. (1998). Baseline salivary cortisol levels and preconscious selective attention for threat. A pilot study. *Psychoneuroendocrinology, 23*(7), 741-747.

Van Honk, J., Tuiten, A., Van den Hout, M., Koppeschaar, H., Thijssen, J., De Haan, E., et al. (2000). Conscious and preconscious selective attention to social threat: different neuroendocrine response patterns. *Psychoneuroendocrinology, 25*(6), 577-591.

Van Osch, M. J., Teeuwisse, W. M., Van Walderveen, M. A., Hendrikse, J., Kies, D. A., & Van Buchem, M. A. (2009). Can arterial spin labeling detect white matter perfusion signal? *Magn Reson Med, 62*(1), 165-173.

Van Zijl, P. C., Hua, J., & Lu, H. (2012). The BOLD post-stimulus undershoot, one of the most debated issues in fMRI. *Neuroimage, 62*(2), 1092-1102.

Vogt, B. A. (2005). Pain and emotion interactions in subregions of the cingulate gyrus. *Nat Rev Neurosci, 6*(7), 533-544.

Vuilleumier, P. (2005). How brains beware: neural mechanisms of emotional attention. *Trends Cogn Sci, 9*(12), 585-594.

Vuilleumier, P., & Pourtois, G. (2007). Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging. *Neuropsychologia, 45*(1), 174-194.

Wang, J., Aguirre, G. K., Kimberg, D. Y., Roc, A. C., Li, L., & Detre, J. A. (2003). Arterial spin labeling perfusion fMRI with very low task frequency. *Magn Reson Med, 49*(5), 796-802.

Wastling, S. J., O'Daly, O., Zelaya, F. O., Howard, M., Alsop, D. C., & O'Gorman, R. L. (2009). Quantitative comparison of methods for spatial normalisation of CASL perfusion MR images. *Proc Intl Soc Mag Reson Med, 17*.

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci, 18*(1), 411-418.

Whitfield-Gabrieli, S., & Ford, J. M. (2012). Default mode network activity and connectivity in psychopathology. *Annu Rev Clin Psychol, 8*, 49-76.

Wiens, S., & Öhman, A. (2002). Unawareness is more than a chance event: comment on Lovibond and Shanks (2002). *J Exp Psychol Anim Behav Process, 28*(1), 27-31.

Wolf, R. L., & Detre, J. A. (2007). Clinical neuroimaging using arterial spin-labeled perfusion magnetic resonance imaging. *Neurotherapeutics, 4*(3), 346-359.

Wong, E. C. (1999). Potential and pitfalls of arterial spin labeling based perfusion imaging techniques for MRI. In C. T. W. Moonen & P. A. Bandettini (Eds.), *Functional MRI* (pp. 63-69). Heidelberg: Springer.

Wright, C. I., Fischer, H., Whalen, P. J., McInerney, S. C., Shin, L. M., & Rauch, S. L. (2001). Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli. *Neuroreport, 12*(2), 379-383.

Yin, Y., Li, L., Jin, C., Hu, X., Duan, L., Eyler, L. T., et al. (2011). Abnormal baseline brain activity in posttraumatic stress disorder: a resting-state functional magnetic resonance imaging study. *Neurosci Lett, 498*(3), 185-189.

Zarahn, E., Aguirre, G. K., & D'Esposito, M. (1997). Empirical analyses of BOLD fMRI statistics. I. Spatially unsmoothed data collected under null-hypothesis conditions. *Neuroimage, 5*(3), 179-197.

Curriculum vitae

PERSONAL DATA

Name	Yolanda Schlumpf
Date of Birth	30.01.1979
Place of Origin	Mexico City
Nationality	Swiss

EDUCATION

07/2009 – 09/2012	University of Zurich, Switzerland Institute of Psychology Division of Neuropsychology *PhD project: The Brain in Dissociative Identity Disorder: Reactions to Subliminal Facial Stimuli and a Task-Free Condition* *International PhD program in neuroscience (Neuroscience Center Zurich)*
01/2012 – 12/2012	University of Zurich, Switzerland Institute of Psychology *Member of the Peer Mentoring Group „Psycho-physiology“*
11/2007 – 10/2009	University of Zurich, Switzerland *Master of Advanced Studies in Neuropsychology (Prof. Dr. Jäncke)*
10/1999 – 12/2004	University of Zurich, Switzerland Institute of Psychology *Master of Science (Psychology, Psychopathology, Religious Science)*

EMPLOYMENT HISTORY

04/2008 – 03/2009	Psychiatric University Hospital Zurich, Switzerland Hospital for Psychogeriatric Medicine

Neuropsychologist

01/2006 – 06/2006 Psychiatric University Hospital Zurich, Switzerland
Ward for Dual Diagnoses Patients

Assistant Clinical Psychologist

PUBLICATIONS

Schlumpf, Y.R., Nijenhuis, E.R.S., Chalavi, S., Weder, E.V., Zimmermann, E., Lüchinger, R., La Marca, R., Reinders, A.A.T.S., & Jäncke, L. (2013). Dissociative part-dependent biopsychosocial reactions to backward masked angry and neutral faces: An fMRI study of dissociative identity disorder. *NeuroImage: Clinical, 3,* 54-64.

Schlumpf, Y.R., Reinders, A.A.T.S., Nijenhuis, E.R.S., Lüchinger, R., Van Osch, M.J.P, & Jäncke, L. (in preparation). Dissociative part-dependent resting-state activity: A controlled fMRI perfusion study of dissociative identity disorder.

INVITED TALKS

Schlumpf, Y.R. (2010, Januar). *MRT-Studie mit DIS-Patienten*. ESTD-Tagung, Universität Bern, Bern.

Schlumpf, Y.R. (2011, November). *Gibt es Multiple Persönlichkeiten? Aktuelle biopsychologische Befunde*. 3. Dialogtagung der Arbeitsgemeinschaft für Verhaltensmodifikation Schweiz (AVM-CH), Epilepsie-Klinik, Zürich.

Schlumpf, Y.R. (2012, Januar). *Vorbewusste mentale Vermeidung von bedrohlichen Reizen. Eine fMRT-Studie mit DIS-Patienten*. ESTD-Tagung, Universität Bern, Bern.

POSTER/ABSTRACTS

Schlumpf, Y.R., Nijenhuis, E.R.S., Chalavi, S., Weder, E.V., Zimmermann, E., Reinders, A.A.T.S., & Jäncke, L. (2011, November). *Preconscious processing of perceived threat in patients with a dissociative identity disorder. An fMRI study.* Poster presented at the 28th ISSTD Annual Conference, Montréal, Canada.

Schlumpf, Y.R., Nijenhuis, E.R.S., & Weder, E.V. (March, 2012). *Psychobiological reactions to masked neutral and angry faces: A controlled functional MRI study of dissociative identity disorder.* Talk given at the 3rd ESTD Bi-Annual Conference, Berlin, Germany.

Schlumpf, Y.R., Nijenhuis, E.R.S., Chalavi, S., Weder, E.V., Zimmermann, E., Lüchinger, R., La Marca, R., Reinders, A.A.T.S., & Jäncke, L. (June, 2012). *Preconscious processing of perceived threat in patients with a Dissociative Identity Disorder. An fMRI study.* Poster presented at the ZNZ Symposium, Zurich,

Switzerland.

TEACHING

Spring semester 2012	Lecturing the MSc programme in *Neurobiology of psychiatric disorders*
Spring semester 2012	Workshop in *Neurobiology of dissociative identity disorder*

SUPERVISION OF UNDERGRADUATE STUDENTS

2009 – present	5 BSc students
	2 MSc students

RESEARCH GRANTS

07/2009 – 04/2012	Forschungskredit, University of Zurich